Paid Circulation, 24,266

Hale
HOSPITAL LIBRARY
BUY U.S. SECURITY BONDS NOW!

The New England Journal of Medicine

FORMERLY THE BOSTON MEDICAL AND SURGICAL JOURNAL — *Established 1828*

VOLUME 238 • MAY 27, 1948 • NUMBER 22

Annual Oration: Medicine's Responsibility in the Propagation of Poor Protoplasm . . 755
Allen S. Johnson

Chronic Thyroiditis 758
Samuel F. Marshall, William A. Meissner and Delbert C. Smith

Tumors of Salivary-Gland Origin 766
Grantley W. Taylor and Gerald G. Garcelon

The Use of Para-Aminobenzoic Acid in a Case of Rocky Mountain Spotted Fever . . . 769
John O. Niles and George C. Bourne

Massachusetts Medical Society 784
A Hundred Years Ago 785
Massachusetts Department of Public Health . 786
Miscellany 786

Medical Progress: Allergy 770
Walter S. Burrage

Case Records of the Massachusetts General Hospital 776

Editorials:
The Nolen–Miles Bill in Retrospect 782
Millions for Defense 783
Venereal-Disease Control 784

Correspondence 786
Book Reviews 786
Notices xix

Entered as second-class matter, November 16, 1932, at the post office at Boston, Massachusetts, under the Act of March 3, 1879.

The Clinician has the last word

At the Lilly Research Laboratories the final answer to the question, "Shall this new drug be offered to the medical profession?" rests squarely on clinical performance. No matter how promising the results in the laboratory, the clinician has the last word. The therapeutic excellence of any new drug must be definitely established through extensive pharmacologic and clinical investigations before it can bear the Lilly label.

Lilly

ELI LILLY AND COMPANY • INDIANAPOLIS 6, INDIANA, U. S. A.

NEW HAMPSHIRE MEDICAL SOCIETY

OFFICERS FOR 1947-1948

PRESIDENT: JOHN A. HUNTER, Dover

VICE-PRESIDENT: CLARENCE E. DUNBAR, Manchester

SECRETARY-TREASURER: CARLETON R. METCALF, Concord

COUNCILORS: Earl J. Gage, Belknap County, 1948; Arthur W. Burnham, Grafton County, 1948; Walter H. Lacey, Cheshire County, 1949; Emery M. Fitch, Sullivan County, 1949; Henry H. Amsden, Merrimack County, 1950; Timothy F. Rock, Hillsborough County, 1950; Frederick S. Gray, Rockingham County, 1951; Bernard J. Manning, Strafford County, 1951; William M. Bronson, Coos County, 1952; Ralph W. Tuttle, Carroll County, 1952.

TRUSTEES: George C. Wilkins, Manchester, 1948; Howard N. Kingsbury, Hanover, 1949; Samuel T. Ladd, Portsmouth, 1950.

HOUSE OF DELEGATES: Speaker, Donald G. McIvor, Concord; Vice-Speaker, Francis J. C. Dube, Center Ossipee.

DELEGATE TO AMERICAN MEDICAL ASSOCIATION: Deering G. Smith, Nashua.

ALTERNATE DELEGATE, AMERICAN MEDICAL ASSOCIATION: Leslie K. Sycamore, Hanover.

NECROLOGIST: Ralph W. Tuttle, Wolfeboro.

STANDING COMMITTEES

ADVISORY COMMITTEE ON JURISPRUDENCE: Chester L. Smart, Belknap County; W. J. Paul Dye, Carroll County; Robert W. Holmes, Cheshire County; Arthur W. Burnham, Grafton County; David W. Parker, Hillsborough County; Robert J. Graves, Merrimack County; Samuel T. Ladd, Rockingham County; Jeremiah J. Morin, Strafford County; B. Read Lewin, Sullivan County; Carleton R. Metcalf, Concord, *Chairman*.

AMENDMENTS TO CONSTITUTION AND BY-LAWS: W. J. Paul Dye, Loren F. Richards, J. E. Larochelle.

CHILD HEALTH: Thomas B. Walker, Ursula G. Sanders, Marion Fairfield.

CONTROL OF CANCER: George C. Wilkins, Ralph E. Miller, George F. Dwinell, Walter H. Lacey, Albert Oppenheimer.

COUNCIL OF NEW ENGLAND MEDICAL SOCIETIES: Carleton R. Metcalf, John A. Hunter, Ralph W. Tuttle.

INDUSTRIAL HEALTH: David W. Parker, Henry Almond, Robert J. Graves.

MATERNITY AND INFANCY: Robert O. Blood, Benjamin P. Burpee, James Sanders.

MEDICAL ECONOMICS: Leslie K. Sycamore, Richard W. Robinson, Francis J. C. Dube.

MEDICAL EDUCATION AND HOSPITALS: John P. Bowler, James W. Jameson, Samuel M. Brooks.

MENTAL HYGIENE: Arthur B. Howard, Edward S. Morris, Simon Stone.

NATIONAL EMERGENCY MEDICAL SERVICE: Daniel J. Sullivan, Joseph M. McCarthy, Clarence E. Dunbar, Bernard J. Manning, John C. Eckels.

PUBLIC HEALTH: Donald G. Barton, Harry W. Savage, Hermann N. Sander.

PUBLIC RELATIONS: The President, the Vice-President, the Secretary-Treasurer, Robert J. Graves, Joseph N. Friborg.

PUBLICATION: Carleton R. Metcalf, Samuel J. King, Lester R. Whitaker.

RURAL HEALTH: William F. Putnam, William P. Clough, Jr., Samuel Feiner.

SCIENTIFIC WORK: Carleton R. Metcalf, Robert R. Rix, Sven Gundersen.

TUBERCULOSIS: Robert B. Kerr, Frank G. Seldon, John D. Spring.

HOUSE OF DELEGATES

THE PRESIDENT, ex-officio.

THE VICE-PRESIDENT, ex-officio.

THE SECRETARY-TREASURER, ex-officio.

BELKNAP COUNTY: Samuel Feiner, Ashland; Nathan Brody, Laconia.

CARROLL COUNTY: W. J. Paul Dye, Wolfeboro; Francis J. C. Dube, Center Ossipee.

CHESHIRE COUNTY: Albert C. Johnston, Keene; James M. Ballou, Keene.

COOS COUNTY: Marjorie A. Parsons, Colebrook; Francis M. Appleton, Gorham.

GRAFTON COUNTY: Israel A. Dinerman, Canaan; Leslie K. Sycamore, Hanover; Leslie E. McKinlay, North Haverhill.

HILLSBOROUGH COUNTY: Clarence E. Dunbar, Manchester; Daniel J. Sullivan, Nashua; Samuel Fraser, New Boston; Loren F. Richards, Nashua; Robert R. Rix, Manchester.

MERRIMACK COUNTY: Philip M. L. Forsberg, Concord; Andrew L. MacMillan, Concord; Francis Brown, Henniker.

ROCKINGHAM COUNTY: John W. Blaisdell, Epping; Donald W. Leonard, Exeter; Fred Fernald, Nottingham.

STRAFFORD COUNTY: Raymond R. Perreault, Rochester; Daniel F. McCoy, Dover.

SULLIVAN COUNTY: Donald C. Moriarty, Newport; B. Read Lewin, Claremont.

ANNUAL MEETING, JUNE 2 AND 3, 1948, HOTEL WENTWORTH, NEWCASTLE, N. H.

MEDICAL BOOKS
of all
Publishers

BROWN AND CONNOLLY, Inc.

27 HUNTINGTON AVENUE
BOSTON 16, MASSACHUSETTS
CO 7-1511

DELINQUENT ACCOUNTS
COLLECTED
Ethically — Courteously — Efficiently
Experienced Over 15 Years
Monthly Report Bonded
For particulars call or write
Medical Clearing Bureau, Inc.
110 Tremont Street, Boston, Mass.
HU 2-5570

Firm, Natural Support Need Never Be Sacrificed For ANY Fashion

A functional garment, properly fitted, will mold a figure to the fashion's new requirements without causing displacement of organs.

EVYLYN L. WEIGEL

25 HUNTINGTON AVE. BOSTON 16, MASS. KENMORE 6-2718
MASSACHUSETTS AVE., ROUTE 111 WEST ACTON, MASS. ACTON 504-3

TWO-WAY PROTECTION
Tablets FERROSATE (Kenmore)
(Ferrous Sulfate, gr. iv)
are coated twice to provide a doubly protected Ferrous Sulfate offering these therapeutic advantages:

1 **Inner coating prevents premature oxidation in vivo.**

2 **Outer coating increases palatability and aids in preventing tooth discoloration.**

Write Dept. N5 for professional sample.
Kenmore Pharmacy, Inc.
500 Commonwealth Ave.
Boston, Mass. U.S.A.

The New England
Journal of Medicine

Copyright, 1948, by the Massachusetts Medical Society

Volume 238 MAY 27, 1948 Number 22

ANNUAL ORATION

MEDICINE'S RESPONSIBILITY IN THE PROPAGATION OF POOR PROTOPLASM*

ALLEN S. JOHNSON, M.D.†

SPRINGFIELD, MASSACHUSETTS

THIS unexpected and undeserved honor has made me acutely aware of my lack of fitness to wear even for this short time the mantle that has graced such distinguished predecessors. Some of them have traced with inimitable charm and grace the progress of medicine through the years. Others have granted to you imaginative glimpses of its achievements in the years to come. As neither endowment nor inclination impels me to assume the role of either historian or prophet I shall ask you to consider with me not where we have been, not where we may be going, but where we are today.

Cynics, idealists, and sentimentalists have tried to define the role of the medical practitioner. I think that most of you who are, like me, average doctors from average communities would agree that our purpose is to enable mankind to make more effective adjustments to the harassments of his environment. Whether these stresses be furnished by trauma, bacteria or psychologic tensions will determine which particular exponent of the healing art is chosen. But the ultimate goal of one and all must be the enhancement of man's capacity for environmental adaptation. Let us examine the balance sheet, then, and evaluate our contributions to man's struggle for existence today.

* * *

Only with profound fear and trembling would one hint that bacterial diseases have been brought under control. Men still die of infection, and undreamed of viral and bacterial mutations may lie in wait for us around the corner. But the contemporary triumphs of modern sanitation and preventive medicine, along with chemotherapy and the more recent antibiotics, certainly warrant more optimism in this field than in some others. In the field of trauma, likewise, these advances, as well as the contributions of the physiologist, have done much to augment the achievements of the surgeon.

Our accomplishments in the field of endocrinology are still somewhat clouded by the perplexing variety of clinical manifestations and interrelations of these systems. But the vast unexplored vistas that stretch before us should not lessen our appreciation of the concrete contributions to the control of thyroid, parathyroid and pancreatic disease for which we may pay grateful tribute to a singularly gifted group of Boston clinicians. Equally encouraging progress is being made in the field of sex endocrinology, which, unfortunately, is still sometimes obscured by commercial exploitation and premature notoriety.

Thanks to the firm foundation laid by the metabolic investigations of thirty years ago the study of nutrition has progressed from the consideration of the laboratory subject to include not merely the sick patient but also whole groups and nations suffering from dietary deficiency. The smugness of our attitude toward these accomplishments will depend upon whether we are reviving a few individuals suffering from a specific deficiency or whether we are trying to rehabilitate an entire country. We may delegate to our interns the treatment of the individual pellagrin or the alcoholic patient with polyneuritis. But the great bulk of deficiency disease today reflects the economic status of the group rather than the incompetence of their doctors and as such bids fair to be a problem for governmental administration rather than individual therapy alone.

Current propaganda on cancer might suggest to the uncritical that here is a race in which medical accomplishment is being outstripped by some malevolent force. It is true that the male death rate for cancer has shown some increase for each decade from 20 to 75 years over the past 35 years. For example, the Metropolitan Life Insurance Company reports that the cancer death rate for in-

*Presented at the annual meeting of the Massachusetts Medical Society, Boston, May 25, 1948.

†Visiting physician, Springfield Hospital, Springfield.

sured groups from 45 to 75 years of age rose from 1120 per 100,000 in 1911 to 1530 per 100,000 in 1945.[1] The cancer death rate for all ages rose from 60 per 100,000 in 1900 to 130 per 100,000 in 1940, but it must be remembered that the age group over 45 years, in which the greatest incidence of cancer occurs, increased 67 per cent[2] during the same 40-year period. Furthermore the lay public and the medical profession have grown increasingly cancer conscious during this period, and this fact, coupled with improved diagnostic methods, probably accounts for some of the statistical increase in cancer deaths. Fortunately, there is a more hopeful aspect to the problem, which suggests that our intensive efforts are bearing fruit. During the period from 1911 to 1945, which showed an increase in male deaths from cancer, there was actually a slight decrease in female cancer deaths. And during the past ten years even the male death rate from cancer has begun to level off.[1] In this connection it is interesting to examine the cancer mortality trends for the last 12 years, adjusted to the age distribution of the total population and classified according to the site of the origin of the neoplasm. Whereas in both sexes there is still an annual increase in deaths from cancer of the respiratory tract, there has been a steady decline in deaths due to cancer of the skin, buccal cavity, stomach and liver. Cancer education and improved medical and surgical care have played a large part, but Potter[3] believes that the decrease in deaths from gastric cancer is greater than could be expected from these factors alone. The work of the Kennaways[4] suggests that gastric cancer arising after the second 25 years of life may be predestined by factors to which the body was exposed during the first 25 years. Potter[3] has pointed out that the change in the death rate from gastric cancer began about 1926, some twenty-five years after significant changes took place in the American dietary,[5] and suggests that there may be a causal relation. This raises a new hope of rational prophylaxis, which, with improvements in diagnostic technic and the therapeutic advances implicit in the recent developments of atomic physics, may still further lower the death rate from malignant tumors.

Whether or not we appear to be extending man's span of life will depend somewhat on our point of view. The pediatrician will point with justifiable pride to the fact that the life expectancy of the newborn white male was 64.44 years in 1945 as compared with 48.23 years in 1900. His sister had an even better outlook by several years. At 40 years in 1945 he had thirty years more ahead of him, which was only 3 years more than the 40-year-old male could expect in 1900. But the life expectancy of the 65-year-old man in 1945 was scarcely a year better than that of his father in 1900.[6] It appears that the geriatrists can hardly join in the pediatricians' boasting. Our control of the infectious hazards of childhood and early adult life seems to have had little effect on the wearing-out process. But whereas the death rate from cardiovascular renal disease has risen from 310 per 100,000 in 1900 to 495 in 1940, an increase of 62 per cent, the proportion of the population over 45 years of age has risen during the same period from 17.8 to 26.5 per cent, an increase of 67 per cent.[2] The Metropolitan Life Insurance Company therefore concludes that "The death rate from this group of causes, corrected for the aging of the insured population, dropped virtually 30 per cent (at ages 1 to 74 years) between 1911–1915 and 1940–1944."[7] Although these figures suggest that the current furor about the rising death rate from degenerative vascular disease is misleading, the insignificant increase in expectation of life at 65 years of age today as compared with the figure 45 years ago indicates that immortality is not just around the corner. Perhaps this is just as well. The catastrophic implications of physical immortality stagger the imagination. Already the social and economic dislocations produced by an ever-increasing number of old people in our population is causing concern. Imagine the chaos if the aged never died off while even the puny birth rate attributed to college graduates continued! Of course even the most enthusiastic geriatrist would blanch at this prospect, but he is inclined to be a little vague when asked to what age it would be socially and individually desirable to extend life expectancy if we had it in our power to do so. Perhaps our goal should be the enrichment of living rather than the mere prolongation of life. This appears certainly to be more nearly within our grasp, and our contributions in this direction may atone in part for our failure to render man immortal.

All this, then, and man's ability to exist at extremes of temperature and barometric pressure bear testimony to medicine's contribution to his physical capacity for environmental adaptation. What of his psychologic adjustments? Has his mental and emotional equipment kept pace with the ever-increasing complexity of his environment? Has science, which has increased the psychologic stresses to which he is subject, helped him to develop behavior patterns of comparable effectiveness? The answer to this question will depend a good deal on what sort of measuring stick we use. No one really knows how many maladjusted people there are in his community, though the average practitioner may be inclined to venture a considerably higher estimate at the end of a busy day than at its beginning. But even his casual estimates are dependent on the economic status of his clientele and on his own insight. Rusk[8] has stated that there are eight million people disabled by mental disease in this country, but the usefulness of this figure depends upon one's definition of disability. Selective Service rejections offer a more precise measure

of serious defects in our citizens' mental equipment. During the last eighteen months of the recent war, when the need for dwindling manpower made us progressively less critical of man's frailties, the Selective Service boards rejected 44 per cent of the 5,767,000 examinees; 26.8 per cent of these rejections were for mental disease, 2.6 per cent for mental deficiency, 4.1 per cent for neurologic disorders, and 12.8 per cent for subminimal intelligence.[9] In other words, 46.3 per cent of all men rejected were deemed unfit on neuropsychiatric grounds to participate in the struggle for biologic survival. Not all of these were incapable of earning some sort of living or of making some degree of adjustment to their social group. Many were capable of defending themselves individually in a somewhat protective and paternalistic society. But they were deemed incompetent to participate in any such collective defense as was demanded for our survival as individuals and as a nation. In other words, they could not be relied upon to make up a winning team.

Forty-six per cent may seem like a high figure, but Selective Service boards were certainly not being unduly critical when manpower was so urgently needed. They may have been overzealous during the early part of the war, but this is not borne out by figures for medical discharges from the armed forces. During the three-year period of hostilities (1942–1945), 956,232 enlisted men were separated from the Army on certificates of discharge for disability; 379,486 (39.69 per cent) of these were for neuropsychiatric reasons.[10] During the same period the Navy gave medical discharges to 318,798 Navy and Marine Corps personnel, and 104,735 (32.9 per cent) of these were for neuropsychiatric reasons.[11] In other words, in spite of attempts at preliminary screening by Selective Service boards, which eliminated nearly half of those called up, more than a third of these were rejected later, on admittedly neuropsychiatric grounds. These figures probably err, if at all, on the side of conservatism, for all of us who sat on "survey boards" were well aware of the frankly psychiatric character of many of the visceral symptoms that earned for their hosts a nonpsychiatric discharge.

The apologist will suggest that war is abnormal and no fair test of a man's social usefulness, even though it may well test the fitness of a society to survive. What is the incidence of serious maladjustment in civilian life? It would be interesting if we could examine from the psychiatric standpoint all members of a small town as the United States Public Health Service has recently done from the standpoint of diabetes. What would be the incidence of major mental disease and of the less serious types of neuropsychiatric disorders? At present we can form only a rough estimate of the burden that institutionalized nervous and mental disease imposes on society. In the United States in 1946 the hospitals for nervous and mental diseases had 46 per cent of all the hospital beds, and the general hospitals only 43.7 per cent. During the same year the former provided 232,055,685 treatment days, or 51.3 per cent of the daily patient load, compared to 181,232,355 treatment days given by general hospitals.[12] This cannot be attributed to the effects of the war, since the figures for 1936 show that hospitals for nervous and mental diseases provided 192,147,438 treatment days, representing 59 per cent of the daily patient load for all hospitals. Since then general-hospital beds have increased faster than those of the institutions for nervous and mental diseases, but the proportions are still roughly the same. In Massachusetts in 1946 hospitals caring for feeble-minded, epileptic and mentally diseased patients had 50 per cent of the total hospital beds and carried 56 per cent of the daily treatment load of all hospitals in the Commonwealth at a cost of somewhat over $14,000,000.[13] If we add to the 10,883,205 patient days in these Massachusetts hospitals in 1946 the man days spent in penal institutions, we may have some idea of the magnitude of this problem of maladjustment and the burden on the remaining few of us who have thus far managed to stay out of institutions.

One might conclude that the mental equipment of much of the population has not kept pace in its capacity for appropriate response with the increasing complexity of the environment. We might, for lack of a better scapegoat, blame science for this complexity. Those who have tried to understand a painting by Dali or the writings of Gertrude Stein might feel that the arts, too, must share the blame for this confusion. But these bizarre expressions can be escaped, unlike the noise of machinery, the speed of traffic, the split-second timing of assembly-line technic and the stresses, both social and economic, of a highly competitive society.

Has science attempted to atone for its responsibility by assisting the less well endowed to make more adequate adjustments? Certainly, the acknowledgment of this responsibility is reflected in the growth of psychiatric clinics, special schools for the handicapped, personnel councilors and so forth, but they reach a relatively small proportion of the needy. Much of the expenditure in the field of nervous and mental disease today is allocated to mere custodial institutional care. It is probably true that these misfits are cared for more cheaply, more effectively and with less risk to society than if allowed to run loose. It is open to question whether all these institutions are indoctrinated with the idea of rehabilitation. It is certain that the scanty budgets of many make it almost impossible. As a result many patients are released as soon as they are no longer an obvious menace to themselves or their social contacts although little has been done for long-range rehabilitation. The question may some day be raised

whether this protection and perpetuation of poor protoplasm by humanitarian institutions is handicapping society as a whole both economically and genetically. Sooner or later, if present trends continue, society will have to develop methods for enabling this growing horde to effect more adequate social adjustments or else take steps to reduce their appalling fecundity. It is an interesting commentary on our social organization that two antithetical forces like war and humanitarian institutions should protect the unfit at the expense of the fit. Yet we stage a war every twenty-five years and demand that only the physically fit and psychologically well adjusted be allowed the privilege of dying for their country. The unfit are protected to perpetuate the race. The inadequate personality is sustained inside and outside institutions by a variety of federal, state and municipal agencies. Even an indisposition to work seldom results in starvation. The unfit is not wanted by the Selective Service board, and even if he leaks through its widemeshed screen and withstands the imprecations of his superiors he is seldom assigned to dangerous or fatal duty because he is incompetent and irresponsible. He may be shorn of prestige and material goods, but his voting and procreative powers remain unimpaired and he and his multitudinous offspring bid fair to be with us always and in ever-increasing numbers. Not all of them can be institutionalized, and not all of them need to be. But they and their problems of adjustment to society constitute a real if unrecognized task to which medicine must shortly apply itself if our contributions to man's psychologic adjustments are to keep pace with our contributions to his physical adaptations.

References

1. Recent progress in cancer control. *Statist. Bull. Metrop. Life Insur. Co.* **26**:6-8, March, 1945.
2. Dublin, L. I. Problems of aging population. *Am. J. Pub. Health* **37**: 152-155, February, 1947.
3. Potter, E. A. Changing cancer death rate. *Cancer Research* (in press).
4. Kennaway, E. L., and Kennaway, N. M. Some factors affecting carcinogenesis. *Acta, union internat. contre cancer* **2**:101-134, 1937.
5. United States Department of Agriculture. *Food and Life: Yearbook of agriculture, 1939.* 1165 pp. Washington, D. C.: Government Printing Office, 1939. P. 10.
6. Longevity in United States at new high in 1945. *Statist. Bull. Metrop. Life Insur. Co.* **28**:3-5, April, 1947.
7. Large decline in mortality from degenerative diseases. *Statist. Bull. Metrop. Life Insur. Co.* **27**:5-8, March, 1946.
8. Rusk, H. Way to better medical care. *New York Times Magazine*, June 29, 1947. P. 12.
9. Editorial. Physical examination of Selective Service registrants in final months of war. *J. A. M. A.* **133**:854, 1947.
10. Office of the Surgeon General of the Army, Washington, D. C. Personal communication.
11. Bureau of Medicine, Navy Department, Washington, D. C. Personal communication.
12. Editorial. Hospital service in United States. *J. A. M. A.* **133**:1155, 1947.
13. Department of Mental Health, Commonwealth of Massachusetts. Personal communication.

CHRONIC THYROIDITIS*

Samuel F. Marshall, M.D.,† William A. Meissner, M.D.,‡ and Delbert C. Smith, M.D.§

BOSTON

CHRONIC thyroiditis, as evidenced by degeneration and fibrotic changes in the thyroid gland, is not a common disease entity but is encountered fairly frequently by the clinician and surgeon experienced in thyroid disease. The recognition of this pathologic process in the thyroid gland is important from the clinical aspect because its firmness, adherence and increase in size of the gland may cause it to be mistaken for malignant neoplasm arising in the thyroid gland.

Classification of this type of thyroid disease has always been more or less troublesome, and loosely used and poorly defined terminology has contributed in no small way to the confusion and disagreement regarding thyroiditis.

More than half a century has passed since Bernhard Riedel,[1] a German surgeon in Jena (1896), presented his original report on the condition of the thyroid gland that has since retained his name and has come to be known as Riedel's struma. Sixteen years later, Hashimoto[2] reported what he considered to be a distinctly separate clinical and pathologic entity, struma lymphomatosa. Since these original reports, many articles have appeared in the literature concerning chronic thyroiditis, but little has been added to the knowledge of its etiology. Likewise, the clinical and pathologic picture, as known today, has changed little from the original descriptions.

Riedel[1] pointed out in his first report of 2 cases that the gland was of woody hardness and densely adherent to the trachea and surrounding blood vessels and nerves, all of which made it difficult to distinguish from a malignant lesion.

Hashimoto's[2] original report consisted of 4 cases, all in women over forty years of age, who presented essentially the clinical picture as it is known today. He was aware of the absence of inflammatory reaction and the lack of adherence to surrounding structures. He went further to point out the postoperative picture of myxedema, which disappeared after the internal administration of thyroid substance. The chief pathologic findings described were diffuse lymphocytic infiltration, atrophy of

*Presented at the annual meeting of the New England Surgical Society Providence, Rhode Island, October 3, 1947.

†Surgeon, Lahey Clinic; surgeon, New England Deaconess and New England Baptist hospitals.

‡Member, Department of Pathology, New England Deaconess Hospital.

§Fellow in surgery, Lahey Clinic.

the acinar epithelium, with absence of colloid, and proliferation of connective tissue.

Despite the clarity with which these authors described two distinctly separate clinical entities, much confusion has occurred. This has been the result of the many variants in the microscopical picture as well as in the clinical findings. The purpose of this paper is not to give a historical review of the numerous controversies existing over the years or of the literature, but to present a summary of a pathological and clinical study of a group of cases encountered in which operation was performed at the Lahey Clinic during the period of 1928 to 1946, inclusive. As every surgeon knows, these cases may present some perplexing problems in technic at the operating table. The present study was undertaken with the hope that certain conclusions could be reached from the observation of a fairly large series of cases that would be of value in the diagnosis and further management of these patients.

During the eighteen-year period under consideration 187 cases of undoubted chronic thyroiditis were encountered in the pathological examination of the specimens from approximately 25,000 patients requiring thyroidectomy. There were many other cases in which a tentative diagnosis of thyroiditis was made on the excised tissue, but since a careful pathological review and reclassification of these specimens revealed them to be lacking in many of the characteristics thought necessary to establish this diagnosis, they were discarded in the study of this material. Also, no cases of thyroiditis occurring in hyperplastic goiter, adenomatous goiter or thyroid tumor are included, although the condition may complicate such already diseased glands. It is evident that this condition is by no means rare, since this represents an incidence of 0.75 per cent. These 187 cases, selected after careful correlation of the clinical findings with the microscopical picture, form the basis of our report.

Many other cases were found in which a clinical diagnosis of thyroiditis was made, but these patients were not submitted to operation, so that pathological examination could not confirm the accuracy of this diagnosis and, of course, they cannot be included in this study. There can be no doubt that with sufficient experience in the disease a fairly large number of cases can be recognized clinically and that, in the event of no complications, operation can safely be avoided. Because of enlargement of the thyroid gland, development of pressure symptoms, constriction of the trachea or inability definitely to exclude cancer, however, a certain number of patients must submit to operation either to decompress the trachea or to rule out malignant degeneration. Some of these patients came to surgery with enlarged thyroid glands that were mistakenly construed by the clinician to be adenomatous goiter. A correct preoperative diagnosis of thyroiditis in the group of 187 cases was made in only 44 patients, or 23.5 per cent, so that the preoperative error in diagnosis of patients submitted to operation is considerable. It is also well to emphasize the fact that the uncertainty regarding the type of thyroid disease present necessitates biopsy or resection of the thyroid gland, and this very fact accounts for the low percentage of correct preoperative diagnosis in this group of operated cases. In many cases the pathologist has difficulty diagnosing the condition correctly without microscopical study. Dr. Frank H. Lahey has often described the characteristics that enable thyroiditis to be recognized clinically in a large number of cases, but the necessity for repeated periodic examinations has also been constantly emphasized. Operation is demanded when even the slightest suspicion of a malignant lesion exists, and progressive enlargement or constrictive symptoms occurring in a previously clinically recognized thyroiditis may also require surgical interference at some time after the initial diagnosis has been established.

Pathology

Concerning the pathology of the various forms of thyroiditis it should be pointed out that there are apparently several ways in which the gland may react to injury or irritation. These basic types of reaction are seen whether the injury is the result of actual infection, trauma, vascular disturbances or altered physiology. Either the stroma or the epithelium of the thyroid gland may show considerable change in response to irritation or injury. The stromal changes consist of fibrosis and infiltration with inflammatory cells, of either mononuclear or polymorphonuclear type. The epithelial changes consist of diminution in the size or atrophy of the acini, acidophilia of the thyroid cells to become the Hürthle type and occasionally epidermidization of the epithelium. At times colloid is allowed to spill out of the follicle into the stroma; since colloid is an irritant, it causes an inflammatory response, with a foreign-body, giant-cell reaction, when it is free in the stroma.

Examples of such changes are seen in the pathologic states of hyperplasia, adenomatous goiter and tumor. In hyperplasia there is frequently an infiltration with lymphocytes and often the formation of secondary lymph follicles. A small amount of fibrosis often accompanies the lymphoid infiltration, particularly in the later stages of involution. The so-called "exhaustion atrophy" of the thyroid gland is a state that presumably follows overactivity, and in this condition there is not only infiltration with lymphocytes and some fibrosis but also frequently an acidophilia of the epithelium.

In adenomatous goiter, fibrosis of the gland owing to hemorrhage or colloid spillage is frequent. Not uncommonly lymphoid infiltration and compression of the acini adjacent to the capsule of the

tumor are found in adenomas. In malignant tumors there is, of course, the inflammatory exudate frequent in cancers.

At times the thyroid gland is the site of similar basic inflammatory changes, which apparently are not associated with hyperplasia, adenomatous goiter or tumor. It is this group, called chronic thyroiditis, with which the present study is involved; cases

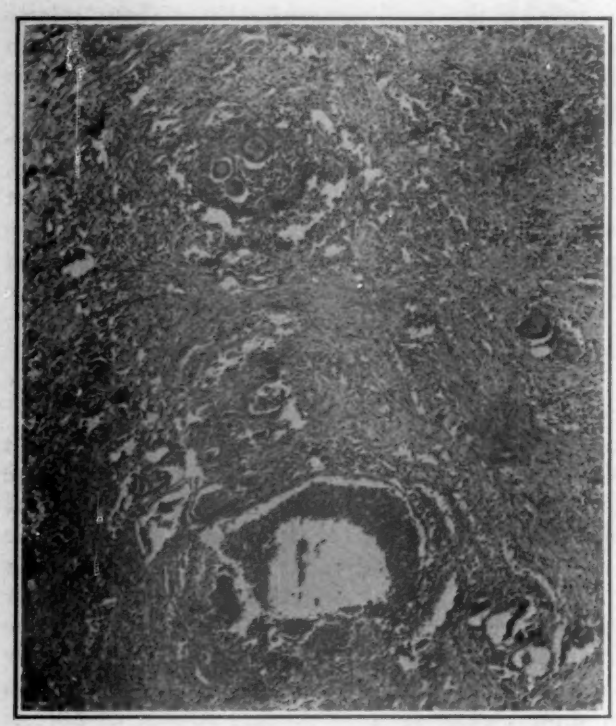

FIGURE 1. *Infection of the Thyroid Gland in the Subacute Stage in a Forty-Six-Year-Old Man Who Complained of Pain and Swelling in the Thyroid Region of Five Weeks' Duration. Note the numerous polymorphonuclear neutrophils in the stroma and in the large acinus at the lower right. Fibrosis and foreign-body giant cells (hematoxylin and eosin, x50).*

that showed a definitive type of pathologic change in addition to inflammation were not included.

Excellent discussions and reviews of the pathology of chronic thyroiditis can be found in detail in the papers of Womack,[3] McClintock and Wright,[4] Joll[5] and others,[6, 7] and a lengthy description is unnecessary here. For the purposes of clinical comparison, it was found that cases of chronic thyroiditis could easily be segregated into three main groups, which were reasonably distinct both pathologically and clinically. The great majority of cases fall fairly easily into one of the three categories. The more important characteristics of each group are described below.

Group I

This group consisted of 41 cases showing a reaction that seemed to be due obviously to infection. It is well known that acute infections of the thyroid gland occur, but since such a gland is not removed surgically in the acute stage of an infection, no acute infections were present in this series. A group of 18 glands, however, showed changes that may be called subacute inflammation (Fig. 1); there was a moderate degree of fibrosis with numerous inflammatory cells, chiefly polymorphonuclear neutrophils often centered in acini. Such acini usually showed degeneration and spillage of colloid with foreign-body, giant-cell response, although the latter cells were not numerous in this stage. In the chronic stage of the infection represented by 18 other specimens (Fig. 2), the polymorphonuclear leukocytes had largely or completely disappeared, but numerous foreign-body giant cells were still present reacting to colloid. Also scattered throughout the fibrotic stroma were numerous lymphocytes and plasma cells. The fibrotic stage of the infection apparently represents the healed stage

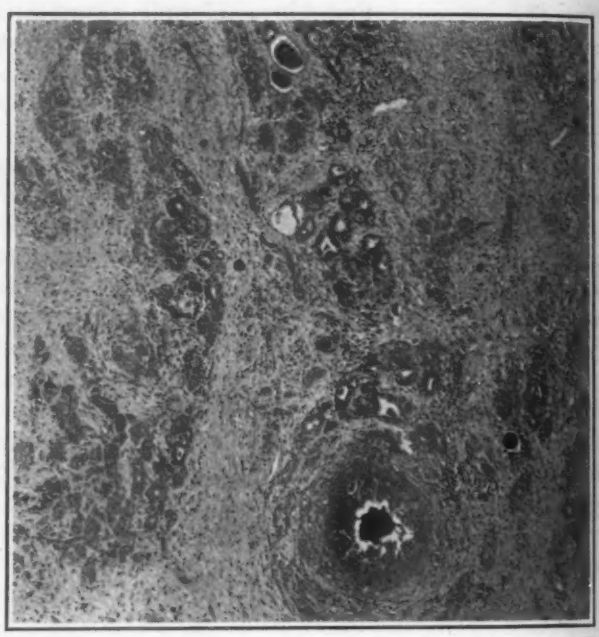

FIGURE 2. *Infection of the Thyroid Gland in the Chronic Stage in a Thirty-Seven-Year-Old Woman Who Had Soreness and Enlargement in the Neck for Four Weeks and a Tonsillectomy for Chronic Tonsillitis One Year Previously.*
Note the numerous foreign-body giant cells (hematoxylin and eosin, x50).

(Fig. 3), and in this terminal phase foreign-body giant cells were usually absent and other inflammatory cells few in number — it is this stage that usually has been designated as Riedel's struma. In none of the stages in this group was the epithelial change characteristic, and although considerable epithelium was apparently destroyed and replaced by the infection and subsequent fibrosis, that which remained usually showed little or no change

and no evident atrophy. Acidophilia was absent or slight; there was occasional epidermidization. Grossly, the glands in this group were all firm, fibrotic and often gray or white. The capsules in most specimens were adherent both to the thyroid gland and presumably to the adjacent structures, since they were infiltrated microscopically with the inflammatory process. The change in the gland was sometimes focal, but often diffuse.

Group II

The second group was composed of 78 thyroid glands, which were generally designated as Hashimoto's struma or struma lymphomatosa. This group pathologically showed a marked infiltration of the stroma with lymphoid cells and the formation of numerous secondary lymph follicles (Fig. 4). The lymphoid infiltration in these glands was often little more than that seen in many cases of primary

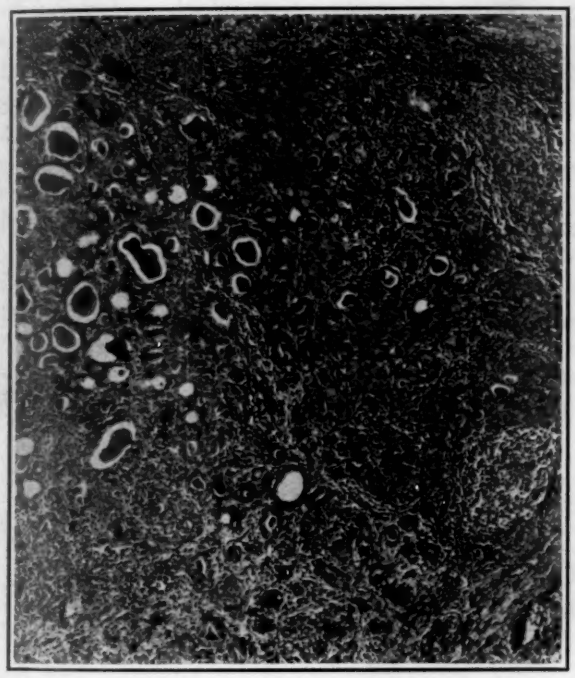

FIGURE 3. *Infection of the Thyroid Gland, Largely Healed, in a Fifty-Two-Year-Old Woman Who Had Had Swelling in the Neck, with Difficulty in Breathing, for Four Years and with Restricted Breathing on Raising the Arms While Combing Hair. Note the marked fibrosis. Many of the remaining acini are little changed (hematoxylin and eosin, x50).*

hyperthyroidism, and such a marked lymphoid infiltrate is not sufficient evidence in itself to warrant placing the gland in this general group. The specimens, in addition to the lymphoid infiltration, uniformly showed atrophy and marked acidophilia of the epithelium. Occasionally there was some degeneration of colloid with foreign-body giant-cell reaction, but this was inconstant. Although the stroma always showed at least a small amount of fibrosis, in small strands and cords, the fibrosis was in broader bands only when pronounced, as in the first group. Grossly the specimens in this category averaged about 100 gm. in weight for the two lobes (Fig. 5). They had a rubbery consistence.

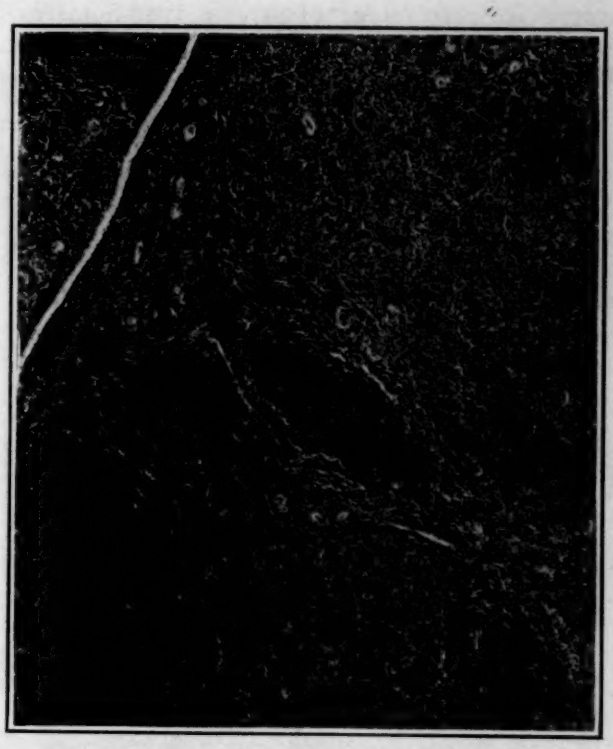

FIGURE 4. *Struma Lymphomatosa in a Forty-Seven-Year-Old Woman Who Had Had Goiter for Three Years, Increasing in Size for the Past Year, with Occasional Coughing and Choking Spells and with Difficulty in Breathing on Exertion. Note the characteristic, marked lymphoid infiltration and atrophy of epithelium (hematoxylin and eosin, x50).*

The change was diffuse and homogeneous throughout both lobes. The capsules were grossly preserved with no suggestion of adherence.

Group III

This was a conglomerate group and undoubtedly included thyroiditis resulting from several causes. The specimens showed little that was characteristic grossly. Microscopically, they showed the basic stromal (slight fibrosis and round-cell infiltration and occasionally spilled colloid) and epithelial (absent or mild acidophilia and atrophy) changes common to all injuries of the thyroid gland, but the changes were of such a mild degree that a further classification was not possible. It seemed best to designate this group of 68 cases as simply "chronic thyroiditis, nonspecific." Two cases of thyroiditis presumably due to irradiation and 1 case of probable syphilis of the thyroid gland were not included. There were no examples of tuberculosis of the gland.

Some of the thyroid glands in this group appeared similar to the "exhaustion atrophy" state, although a history of previous hyperthyroidism was unusual. Other glands suggested that the inflammatory response was the result of a mild infection, which was not severe enough to warrant inclusion in Group I. Still other specimens must have represented an early stage of struma lymphomatosa, but with changes too mild to be pathognomonic. Vascular changes were considered a possibility as

FIGURE 5. *Struma Lymphomatosa in a Sixty-One-Year-Old Woman Who Complained of Marked Swelling in the Neck of One Year's Duration.*

Note the lobulation and the thin capsule.

an etiologic factor in this group, but no changes could be found that could be directly attributed to vascular lesions. Still another etiologic possibility is trauma.

It is possible, then, to divide chronic thyroiditis into three groups pathologically. Group I includes cases of thyroiditis in the true sense — that is, inflammation of the thyroid gland caused by actual infection. The terminal or healed stage of this type of thyroiditis has been known as Riedel's struma, but it seems more logical to include all stages of infection of the thyroid gland under one grouping no matter whether the infection is acute, subacute, chronic or healed. Group II, composed of specimens that have previously been designated as struma lymphomatosa, appears to be distinct and separate from thyroiditis caused by infection. The pathological changes are characteristic enough in most cases to warrant a separation of these specimens from the other types of thyroiditis, although the etiology is unknown. In addition to these two groups, which present more or less specific pictures pathologically, there is the third group of rather indefinite mild inflammatory changes, which must be designated as nonspecific chronic thyroiditis.

SYMPTOMS

The outstanding symptoms presented by patients with chronic thyroiditis in this series were more or less similar in all three groups of cases. The most common complaint was that of goiter or enlargement of the neck (Table 1), and was the initial complaint of 80 per cent of the patients. Local manifestations of thyroid disease were pressure symptoms, breathing difficulties, choking sensation and difficulty in swallowing in a much smaller percentage, and were present in the majority of the more advanced or more chronic cases. Neck discomfort was outstanding in the cases of infection thyroiditis (Group I), occurring in 1 in 4, and this is to be expected in view of the marked tendency to fibrosis and constriction in this type of thyroiditis. Alteration of the general physical condition, which was not a prominent feature unless myxedema was present and which occurred infrequently in the form of nervousness or fatigue, was observed more often in patients with a strong tendency to neurosis or phobia of cancer. The average duration of symptoms in all groups was approximately two years.

Diagnosis is established by the presence of an increase in size of the thyroid gland. It may be fairly large (two to four times the size of the normal gland) and firm, and this feature is characteristic of all three groups. The enlargement is bilateral in the majority of cases (occasionally it is unilateral in Reidel's struma) and is symmetrical. The anatomic outline of the lobes is maintained, as is the sharp apex of the upper pole where the superior thyroid vessels enter. The firmness of the gland in Riedel's thyroiditis may be very marked; it is woody or stony hard, with a tendency to adherence to the trachea and surrounding structures, and gives to the examiner a sensation of immobility. The induration of struma lymphomatosa is more elastic and resilient but still quite firm; it is not accompanied by the adherence to surrounding structures noted in the first group. The differentiation from

TABLE 1. *Presenting Symptoms in Cases of Chronic Thyroiditis.*

SYMPTOM	GROUP I NO. OF CASES	GROUP II NO. OF CASES	GROUP III NO. OF CASES
Goiter or enlargement in neck	30	66	53
Difficulty in breathing	4	12	4
Pressure sensation	3	10	11
Nervousness	8	8	6
Fatigue	9	7	4
Cough	2	6	3
Hoarseness or change in voice	4	6	4
Discomfort in neck	10	4	3
Choking sensation	0	4	7
Difficulty in swallowing	2	3	7

cancer in the majority of cases of all groups can be made readily, but it is well to point out that cancer cannot definitely be ruled out in a small percentage of cases, and these patients must submit to surgical interference consisting of either biopsy or partial resection of the gland. Thyroiditis usually arises in a presumably normal gland, which has not previously been the seat of a goiter, and no marked lymphoid infiltration with little or no secretive epithelium of Hashimoto's struma represents the healed or end stage of the process in these two groups. There is no evidence that in the chronic stage of thyroiditis acute inflammatory changes will develop. Fever does not accompany the process of chronic thyroiditis, and signs of inflammation such as redness and marked tenderness

TABLE 2. *Data in Cases of Thyroiditis Due to Infection (Group I).*

Stage of Thyroiditis	No. of Cases	Age of Patients			Sex of Patients		Average Duration of Symptoms	Correct Preoperative Diagnosis	Cases of Preoperative Hypothyroidism	Cases of Postoperative Hypothyroidism	Cases of Postoperative Complications		
		Youngest	Oldest	Average	Male	Female					Tracheotomy	Tetany	Recurrent-laryngeal-nerve paralysis
		yr.	yr.	yr.			mo.	%	%	%			
Subacute	18	36	53	44	4	14	2.2	55	–	11	–	–	1
Chronic	16	29	70	46	6	10	6.0	63	6	37	–	–	–
Healed	7	26	63	49	1	6	23.0	43	29	57	–	1	–
Totals	41				11	30					–	1	1
Averages		26	70	46			9.6	56	7	27			

history of nodular goiter can be obtained. Carcinoma arises commonly on the basis of an adenoma, and consequently the gland is usually nodular from the beginning. As the malignant growth involves and breaks through the capsule, the gland loses its anatomic outline and symmetry, and ordinarily the neoplasm involves one lobe or the isthmus and the fixation is local over the tumor and does not possess the symmetrical fixation of Riedel's thyroiditis. If the clinical diagnosis of thyroiditis can be reasonably assured or if a biopsy specimen

in the neck are not described nor have we been able to obtain the history of such local inflammation in any of the cases in this group. Spontaneous regression of the inflammatory process probably also does not occur.

Sex Distribution

It is well known that the thyroiditis described by Hashimoto is rarely seen in men, and in the group of 78 cases, only 1 occurred in a male patient (1 male to 77 females), whereas infectious thyroiditis

TABLE 3. *Data in Cases of Struma Lymphomatosa (Group II).*

Degree of Thyroiditis	No. of Cases	Age of Patients			Sex of Patients		Average Duration of Symptoms	Correct Preoperative Diagnosis	Cases of Preoperative Hypothyroidism	Cases of Postoperative Hypothyroidism	Cases of Postoperative Complications		
		Youngest	Oldest	Average	Male	Female					Tracheotomy	Tetany	Recurrent-laryngeal-nerve paralysis
		yr.	yr.	yr.			mo.	%	%	%			
Mild	12	29	58	45	—	12	23	—	—	50	—	1	—
Moderate	36	31	71	52	—	36	24	14	11	77	1	—	2
Marked	30	33	69	51	1	29	28	27	7	93	1	1	3
Totals	78				1	77					2	2	5
Averages		29	71	50			26	17	8	79			

is obtained to establish the absence of neoplasm, there is no evidence that the malignant degeneration is likely to develop in a gland involved with thyroiditis. The various stages of degenerative and fibrotic changes noted on pathological study in Groups I and II may well indicate that the disease is progressive in character and that the advanced sclerotic, woody gland of Riedel and the

(Group I) may occur in either the male or the female (Tables 2 and 3). About half the cases in the literature are said to have occurred in men; in our series there were 11 males to 30 female patients. In the cases of nonspecific thyroiditis (Group III) there were 3 males and 65 female patients (Table 4). We have no data to indicate whether the sex distribution in these cases was significant, but since thyroid

disease is more common in women, the tendency of greater incidence in female patients may not be especially helpful in diagnosis of thyroiditis and may not be especially significant. In view of the infrequency of Hashimoto's thyroiditis in men, however, it is extremely unlikely that a preoperative diagnosis of struma lymphomatosa could be made correctly in men.

TABLE 4. *Data in Cases of Nonspecific Thyroiditis (Group III).**

No. of Cases	Age of Patients			Sex of Patients		Average Duration of Symptoms	Correct Preoperative Diagnosis	Cases of Preoperative Hypothyroidism	Cases of Postoperative Hypothyroidism
	Youngest	Oldest	Average	Male	Female				
	yr.	yr.	yr.			mo.	%	%	%
68	12	75	43	3	65	22	12	6	50

*No postoperative complications occurred in this group of cases.

Age

The average ages for the three groups of cases were essentially similar and were not especially significant. Thyroiditis of the infectious type or of the Hashimoto type is rarely seen before the age of thirty-five, but may occur at any age thereafter (Table 2).

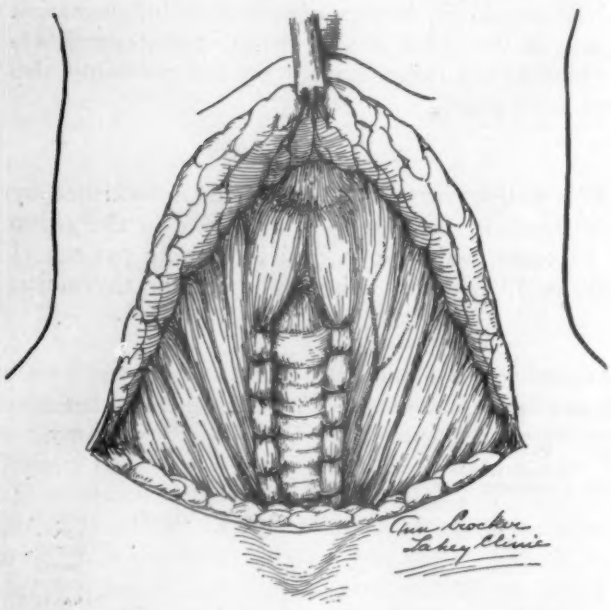

FIGURE 6. *Stage in Operation for Chronic Thyroiditis. The isthmus and medial portions of both lobes have been removed to clear the anterior part of the trachea of all thyroid tissue. The sternohyoid muscles have been sutured to the trachea to prevent adherence of the lateral lobes and recurrence of compression.*

Treatment

We have already called attention to the fact that diagnosis can be made in a large number of cases and that treatment in many cases is unnecessary, but these patients should be observed at stated intervals for evidence of compression of the trachea and to exclude the possibility of overlooking malignant tumors. If treatment is indicated in any case, we believe that operation offers the best method. It should consist of either partial resection of the gland or excision of the isthmus to relieve constriction of the trachea. We have not treated any of these patients with irradiation although there are some reports of good results in the literature. We believe that additional fibrosis produced by the reaction of irradiation may well increase the constriction on the trachea and also further destroy remaining thyroid-secreting epithelium. The principal indications for surgery are definite pathologic evidence that the process is not malignant and relief of pressure symptoms or release of tracheal constriction. In most cases of Riedel's thyroiditis the diagnosis can be established at the operating table by the appearance of the thyroid gland upon exposure and by its adherence to surrounding structures, and biopsy can immediately confirm this. Radical resection is unnecessary, and may be difficult because of the stony hardness of the gland and the difficulty in dissection and exposure of the normal structures such as the re urrent laryngeal

FIGURE 7. *Narrowing of the Trachea Caused by Compression from Chronic Thyroiditis (Reprinted from Lahey[8] by Permission of the Publishers).*

nerves and parathyroid glands. If radical removal is persisted in when marked induration and adherence are present, serious complications may result from injury to the parathyroid glands and to the recurrent laryngeal nerves. Furthermore, release of pressure on the trachea can be obtained by simple removal of the thyroid isthmus, as proposed by Lahey,[6] which separates the lobes and releases the vise-like pressure on the trachea. Suture of the prethyroid muscles to the tracheal fascia prevents the lobes from becoming adherent to each other with return of pressure on the trachea (Fig. 6). Inasmuch as active thyroid-secreting epithelium is still present in the sclerosed gland in Riedel's thyroiditis, extensive partial removal is undesirable, since this procedure decreases thyroxin secretion still more and increases the number of cases in which myxedema develops.

Bilateral partial thyroidectomy is advisable in Hashimoto's struma and should be radical enough to relieve the compression (Fig. 7) noted in these cases as well as to improve the cosmetic effect by removal of an enlarged gland. Large remnants of either lobe should be allowed to remain to avoid injury to the recurrent laryngeal nerves or parathyroid glands, although the lack of adherence of the gland precludes much risk. It is evident that a radical resection in these cases will result in earlier signs of myxedema, but many of these patients exhibit hypothyroidism before operation; practically all patients (7 per cent preoperatively and 27 per cent postoperatively in Group 1, 8 per cent preoperatively and 79 per cent postoperatively in Group II and 6 per cent preoperatively and 50 per cent postoperatively in Group III) develop myxedema later regardless of how much thyroid tissue is removed. It matters only that sufficient tissue be removed to relieve pressure symptoms and constriction of the trachea; we believe that this can be done best by a liberal partial thyroidectomy.

Type of Operation

From this discussion, excision of the thyroid isthmus is considered sufficient in most cases of infection thyroiditis, and a partial bilateral thyroidectomy is desirable in struma lymphomatosa. The best procedure in patients in Group III is excision of the isthmus, but this may have to be modified if sufficient relief of pressure cannot be obtained by such a conservative procedure. In these cases, as in Group I, every effort should be made to conserve thyroid tissue to avoid myxedema. The frequency of myxedema in the various groups after the various operative methods may well serve as a guide in planning treatment in these cases.

Thyroid deficiency is present or develops after operation in many cases. It is much less common in the infectious type (27 per cent), but in the more advanced stage of this group (Riedel) it was noted in 57 per cent. As stated above, patients with Hashimoto's struma developed signs of thyroid deficiency in 79 per cent of the whole group, but this incidence was increased only 8 per cent if partial thyroidectomy was done. In the nonspecific group, thyroid deficiency was noted in 50 per cent of cases, but a decreased tendency (33 per cent) was noted with resection of the isthmus only. In some instances too few cases were observed to draw final and definite conclusions, but our studies seem to point to the value of conserving thyroid tissue whenever possible, except possibly in the Hashimoto type.

Postoperative complications consisted of tetany and recurrent-laryngeal-nerve paralysis (Tables 2, 3 and 4); 2 patients required temporary tracheotomy after operation for Hashimoto's struma, but this was necessary because of edema arising after operation in myxedematous patients, which is not an uncommon complication and did not follow nerve injury. In view of the possible tendency for patients with myxedema to develop postoperative edema it is wise to correct any thyroid deficiency by oral administration of desiccated thyroid before operation and thus to avoid respiratory difficulty after operation. We believe that with recognition of the necessity for exposure of the recurrent nerves in all partial resections of the thyroid gland for any cause, the complication of recurrent-laryngeal-nerve paralysis can be avoided or at least seldom encountered.

Summary

A report of 187 cases of chronic thyroiditis is presented, and an attempt is made to analyze the clinical and pathological characteristics.

Chronic thyroiditis occurred not infrequently in our experiences with approximately 25,000 operations for thyroid disease, an incidence of 0.75 per cent.

An attempt is made to classify these cases into three groups on the basis of pathological changes noted in the excised gland and to correlate these findings with the clinical course of the patients.

Clinical diagnosis of chronic thyroiditis is possible, and it is clinically possible to distinguish thyroiditis from thyroid cancer in a large number of cases.

Treatment is unnecessary in many cases but when necessary to establish diagnosis or to relieve pressure on the trachea, surgical removal of the isthmus or partial thyroidectomy offers the best method.

Myxedema develops with the course of the disease, and operation should be planned to minimize this tendency as much as possible.

Operative complications can be avoided or decreased with a better selection of the type of opera-

tion in each case and with improvement in technic of thyroid resection.

References

1. Riedel, B. M. C. L. Die Chronische, zur Bildung eisenharter Tumoren führende Entzündung der Schilddrüse. *Verhandl. d. deutsch. Gesellsch. f. Chir.* 25:101-105, 1896.
2. Hashimoto, H. Zur Kenntniss der lymphomatösen Veränderung der Schilddrüse (Struma lymphomatosa). *Arch. f. klin. Chir.* 97: 219-248, 1912.
3. Womack, N. A. Thyroiditis. *Surgery* 16:770-782, 1944.
4. McClintock, J. C., and Wright, A. W. Riedel's struma and struma lymphomatosa (Hashimoto): comparative study. *Ann. Surg.* 106: 11-32, 1937.
5. Joll, C. A. Pathology, diagnosis, and treatment of Hashimoto's disease (struma lymphomatosa). *Brit. J. Surg.* 27:351-389, 1939.
6. Lahey, F. H. Thyroiditis: operative procedure for relief of tracheal constriction due to thyroiditis. *Surg., Gynec. & Obst.* 60:969, 1935.
7. Riedel, B. M. C. L. Vorstellung eines Kranken mit chronischer Strumitis. *Verhandl. d. deutsch. Gesellsch. f. Chir.* 26:127-129, 1897.

TUMORS OF SALIVARY-GLAND ORIGIN*

Grantley W. Taylor, M.D.,† and Gerald G. Garcelon, M.D.‡

BOSTON

THIS report summarizes the experience with tumors of salivary-gland origin observed at the Massachusetts General Hospital from 1930 to 1941, inclusive, and at the Pondville State Cancer Hospital from 1927 to 1941, inclusive. Table 1 presents the distribution of the cases.

The relative frequency of carcinoma and mixed tumors of the parotid and submaxillary salivary glands is unusually high in this series of cases as shown in Table 1. This is due to the fact that more carcinomas than mixed tumors of the parotid and submaxillary salivary glands were observed at the Pondville State Cancer Hospital during the period studied. A truer incidence of the relative frequency of these tumors is shown in the Massachusetts General Hospital cases, in which there were 91 mixed tumors and 25 carcinomas of the parotid gland and 14 mixed tumors and 8 carcinomas of the submaxillary salivary gland.

Table 1. *Tumors of Salivary-Gland Origin.*

Type of Tumor	Parotid Gland	Submaxillary Gland	Abnormal Locations
	no. of cases	no. of cases	no. of cases
Mixed	115	16	12
Carcinoma	61	12	2
Miscellaneous	17	6	

The miscellaneous group comprises cysts, adenomas, sarcoma, Mikulicz's disease and various other conditions. These tumors cause confusion in diagnosis. They are sufficiently rare so that decision regarding treatment must be made on the merits of the individual case. Our present concern is primarily with the mixed tumors and carcinomas of the parotid and submaxillary salivary glands. Identical tumors may occur in abnormal locations about the mouth and elsewhere, principally in the cheeks, palate or lips. Their management is the same as that of the corresponding tumors of the salivary glands.

Diagnosis

The usual patient presents a symptomless tumor in the submaxillary or parotid region, discovered accidentally or because some fullness or swelling is noted. The differentiation between mixed tumor and carcinoma on the basis of history and physical findings alone is difficult and often impossible. Although the relation of mixed tumor to carcinoma is obscure, the diagnosis of carcinoma arising from mixed tumor was made on pathological study in 10 cases in the present series (16 per cent of the cases of carcinoma). In certain other cases of long duration the pre-existence of a benign tumor may be assumed. Analysis of the preoperative duration disclosed that more than half the mixed tumors were known to be present for over three years, in contrast to the carcinoma cases, in which nearly half the patients gave a history of known duration of a year or less. The mixed tumors are generally characterized as sharply defined, firm rather than hard, and movable. In contrast, the carcinomas are often less sharply defined, are usually described as hard rather than firm and are already fixed in the great majority of cases when the patient is first seen. Whereas both tumors may occur at any age, from the second to the ninth decade, the greatest concentration of mixed tumors takes place in the third and fourth decades, and the carcinomas occur principally in the sixth and seventh. Primary facial-nerve palsy was observed in 15 cases of carcinoma of the parotid gland (25 per cent), but it did not occur in the cases of mixed tumor, although in 1 case there was some twitching of the lip suggesting nerve irritation. Cervical-lymph-node enlargement was noted

*Presented at the annual meeting of the New England Surgical Society, Providence, Rhode Island, October 3, 1947.

From the Massachusetts General Hospital and the Pondville State Cancer Hospital (Massachusetts Department of Public Health).

This study was aided by a grant from the American Cancer Society (Massachusetts Division), Inc.

†Associate in surgery, Harvard Medical School; visiting surgeon, Massachusetts General Hospital; visiting surgeon, Pondville State Cancer Hospital.

‡Graduate assistant in surgery, Massachusetts General Hospital; associate surgeon, Newton-Wellesley Hospital.

in association with 4 cases of mixed tumor of the parotid gland. Established cervical-lymph-node metastases were present in 29 cases (47 per cent) of the parotid carcinomas. Finally, the possibility of remote metastasis should be considered in cases of carcinoma. Pulmonary metastases were discovered in 4 cases of parotid carcinoma primarily, and remote disease in the lungs, skeleton, liver and other areas was observed in 12 more during the later course of the disease. These clinical contrasts between mixed tumors and carcinomas are summarized in Table 2.

TABLE 2. *Clinical Data in Cases of Mixed Tumors and Carcinoma.*

TYPE OF TUMOR	MEDIAN AGE OF PATIENTS	MEDIAN DURATION OF TUMOR	TUMOR OF HARD CONSISTENCE	MOVABLE TUMOR	ENLARGEMENT OF CERVICAL LYMPH NODES	PRIMARY FACIAL-NERVE PALSY	REMOTE METASTASES
	yr.	yr.	%	%	%	%	%
Mixed	30–40	More than 3	30	80	3	—	—
Carcinoma	50–60	Less than 1	80	15	47	25	25

It is evident from these data that in many cases the diagnosis on clinical evidence is ambiguous and that exploration must be resorted to. At the time of operation the discovery of lack of definition of the limits of the tumor, the persistence of fixation as the operation progresses and the apparent implication of the branches of the facial nerve in the tumor itself all argue for the probable diagnosis of cancer. In cases of doubt, it is necessary to resort to immediate pathological examination.

TREATMENT

Mixed Tumors

In recent years there has been increasing recognition that simple enucleation of mixed tumors invites the possibility of recurrence and that simple enucleation of a tumor that proves to be carcinoma destroys the best chance of effecting a cure. The present practice is essentially that described by Adson and Ott,[1] in which the facial nerve is identified and exposed, and the part of the gland lying superficial to the nerve, including the tumor, is completely removed. In the cases in which the mixed tumor originates in the part of the gland lying on the deep medial aspect of the nerve, the nerve and its branches may be lifted to permit removal of the tumor-bearing area.

There were 94 primary cases of mixed tumor of the parotid gland and 21 cases with recurrent tumors after primary treatment elsewhere. Eighty-five patients with primary cases were treated by surgery, of whom 8 developed recurrences and 6 had some facial-nerve injury. Of 19 patients with recurrent tumors submitted to operation, 3 had already suffered injury to the facial nerve. Four secondary cases developed later recurrence, and an additional patient suffered facial-nerve injury. Among 15 primary and 10 recurrent cases treated by the Adson–Ott operation described above there were no recurrences or facial palsies in the primary cases, whereas there were 3 recurrences and 1 facial palsy in the recurrent cases.

The relatively large number of patients who first present themselves at the clinics with recurrence following operation elsewhere suggests that enucleation of the tumors is rather widely followed, and that it is associated with considerable risk of recurrence and facial-nerve injury. Our own experience with simple excision or enucleation (61 cases with 5 recurrences and 3 cases of facial palsy) confirms the unsoundness of this method of management. Although some patients were treated with incomplete excision supplemented with radiation, we had no significant success with this method. However, our experience is too limited to permit evaluation of the various proposed technics of radiation as supplementary or definitive therapy for mixed tumors..

Several years ago McFarland[2] suggested that mixed tumors may become increasingly benign with time and growth, and that recurrence is less likely to follow operation on large tumors of long duration than operation on small tumors. Analysis of the present group in respect to size of the tumor in relation to the incidence of recurrence does not support McFarland's contention. In fact, the highest incidence of local recurrence was associated with the largest primary tumors.

There were 8 recurrences among the primary cases subjected to operation (10 per cent). All these followed operative technics that have since been discarded. All patients were submitted to a second operation, which was successful in all but 1 case, in which a third operation was necessary to effect a cure. Among the patients with secondary cases subjected to operation, there were 4 (20 per cent) in whom a recurrence took place after operation, requiring a third operation for control.

It seems unnecessary to labor the point that local recurrence is due to improper surgical technic. There was a definite notation that the tumor was encapsulated in 83 cases, and in 23 of these the tumor capsule was broken or cut into. Follow-up observation on 16 of these patients disclosed recurrence in 4 (25 per cent). There is considerable likelihood that

the incidence of recurrence is greater than these figures indicate, because a long time may elapse before the recurrence is manifested. In nearly half our cases, the recurrence took place after five years.

The mixed tumors of the submaxillary salivary gland are treated in the same way as those of the parotid gland — namely, by radical removal of the gland. Recurrence took place in only 1 case in our series, in which only a small part of the gland had been removed along with the tumor.

Carcinomas

The treatment of carcinoma of the parotid gland depends upon the stage of the disease. In the earliest stage, the tumor is first recognized as carcinoma by the pathologist. Provided that a wide excision of the Adson–Ott type has been employed, there does not appear to be any indication for further operation at the moment. Many such cases are given a course of postoperative x-ray therapy, but review of the material does not suggest that recurrence is avoided or delayed as a result. Careful follow-up observation over a long period will detect cases that develop cervical-lymph-node metastases requiring neck dissection or that present operable local recurrence in the parotid region.

The second stage includes cases in which the diagnosis of carcinoma is made preoperatively or during the course of the operation. These cases call for radical measures at once, with sacrifice of the nerve if it is possibly implicated and with radical neck dissection. Finally, a large number of cases are inoperable when the patients are first seen, owing to wide local fixation, inoperable metastases or remote dissemination. These patients are treated with various operations or combinations of surgery and radiation, depending upon the problem presented by the individual case. The carcinomas are not particularly sensitive to radiation therapy.

The secondary cases in this series fall into two groups, those with recurrence following operation elsewhere, and a smaller group of patients who are sent for prophylactic postoperative radiation. Those with established recurrences are treated essentially like the primary cases of corresponding stage.

Among the 61 cases of carcinoma of the parotid gland, 40 were primary cases, and 21 had received treatment elsewhere. Radical removal of the parotid tumor with or without supplementary radiation, was employed in 33 cases, in which 5 patients were cured, 7 were untraced and the remainder were failures. Radical neck dissection was added to removal of the primary tumor in 7 additional cases, but there were no cures in this group. Seventeen primary cases were treated with radiation alone, with no cures. It is evident that the results of treatment are unsatisfactory and that the principal difficulty is due to the advanced stage of the disease when the patients are first seen. Analysis of the causes of failure indicates that recurrence in the operative field was the principal one, taking place in 19 cases.

There were 12 patients with carcinoma of the submaxillary salivary gland. Ten of these were subjected to surgical treatment, with or without supplementary radiation. There were no cures in this group. Here again there was failure to control the primary disease, rather than metastases. When it is realized that a large percentage of submaxillary-gland tumors are carcinomatous (Table I), the desirability of more radical local interventions is obvious.

There were 2 carcinomas of salivary-gland origin in abnormal locations, 1 involving the palate and the other the antrum. The former case was treated by electrosurgical excision and electrocoagulation, and the other by multiple operations followed by radium and x-ray radiation. Both patients died because of failure to control the disease locally.

Summary

The experience of the Massachusetts General and Pondville hospitals with tumors of salivary-gland origin is reviewed.

The differential diagnosis of mixed tumors and carcinomas is difficult, but certain characteristics permit a presumptive diagnosis.

The treatment of mixed tumors is satisfactory provided that a wide resection of the gland is carried out. Visualization of the facial nerve is the best safeguard against injury. Enucleation of the tumor invites recurrence.

The treatment of carcinoma is unsatisfactory. Failure to establish the diagnosis in early cases results in the employment of subradical procedures and invites recurrence. A large percentage of the patients present advanced and incurable disease when they are first seen. Early wide resection of the gland offers the best chance for cure. In our experience radiation treatment is not effective.

References

1. Adson, A. W., and Ott, W. O. Preservation of facial nerve in radical treatment of parotid tumors. *Arch. Surg.* 6:739-746, 1923.
2. McFarland, J. Three hundred mixed tumors of salivary glands, of which sixty-nine recurred. *Surg., Gynec. & Obst.* 63:457-468, 1936.

Additional Reference

McCormack, L. J., Cauldwell, E. W., and Anson, B. J. Surgical anatomy of facial nerve with special reference to parotid gland. *Surg., Gynec. & Obst.* 80:620-630, 1945.

CLINICAL NOTE

THE USE OF PARA-AMINOBENZOIC ACID IN A CASE OF ROCKY MOUNTAIN SPOTTED FEVER

JOHN O. NILES, M.D.,* AND
GEORGE C. BOURNE, M.D.†

HYANNIS, MASSACHUSETTS

PARA-AMINOBENZOIC acid was first reported in the treatment of louse-borne rickettsial diseases in 1942 by Snyder and his associates.[1] After experimental work on the Rickettsia of Rocky Mountain spotted fever by Hamilton, Plotz and Smadel[2] among others, its subsequent use in the treatment of human beings was reported by Rose et al.[3] and other investigators. The patient in the following case was treated according to a schedule reported by Greeley.[4]

CASE REPORT

A 4½-year-old girl was admitted to the hospital on June 4, 1947, with a history of fever and rash over the upper and lower extremities of 2 days' duration. One week prior to entry wood ticks had been removed by the mother from the child's head. Two days before admission a lump was noted on the back of the child's head. She complained of nausea and abdominal discomfort, and vomited on two occasions on the day prior to admission, and the temperature was 104°F. The child also complained of a headache and chilly sensations. She appeared to be drowsy, restless and irritable when seen by Dr. Carroll Keene, of Chatham, Massachusetts, who advised hospital admission because of a rash suggestive of spotted fever.

The past history was irrelevant; there had been no recent exposure to childhood diseases.

The family history was noncontributory.

Physical examination revealed a well developed and well nourished child, complaining of headache and chills, who was somewhat irritable and delirious. The head was normal except for nontender, cervical lymph nodes in the posterior triangle on the right side. There was no evidence of infection in the scalp or localized areas of hematoma. The eyes and ears were normal. The nose and throat were not remarkable except for a slight, nonpurulent, nasal discharge. The lungs were normal to auscultation and percussion. The heart was normal in size, shape and rhythm. Examination of the abdomen was negative. There were no masses or areas of tenderness. The liver and spleen were not palpable. The extremities were normal. Neurologic examination was essentially negative except for some general hyperactivity. The skin showed a finely macular discrete rash scattered over the upper and lower extremities. It was located mainly below the elbows and knees, becoming more pronounced toward the periphery and was present on the palms of the hands and the soles of the feet. The macules blanched on pressure, and occasional petechiae were also noted. Scattered macules were observed on the chest and neck, and a few on the back and abdomen. None were seen on the face.

The temperature was 102.8°F., the pulse 100, and the respirations 22. The blood pressure was 90/40.

Examination of the blood revealed a red-cell count of 4,500,000, with a hemoglobin of 14.5 gm. per 100 cc., and a white-cell count of 9000, with 68 per cent neutrophils and 32 per cent lymphocytes. Urinalysis showed a specific gravity of 1.032 and negative tests for albumin and sugar, with occasional white cells noted in the sediment. The nonprotein nitrogen was 32 mg., and the blood sugar 140 mg. per 100 cc. The sedimentation rate was 20 mm. in 1 hour (Westergren method). Blood was drawn for agglutination tests for typhoid fever, undulant fever and Weil-Felix reactions. The results are reported below.

The patient was treated symptomatically with fluids and aspirin on admission. Approximately 17 hours after entry, the child was given 5 gm. of para-aminobenzoic acid in 25 cc. of a 5 per cent sodium bicarbonate solution; 60 cc. of pineapple juice was used to disguise the acrid taste of the solution. This, however, was vomited soon after ingestion. The same dosage and preparation were repeated in 2 hours, and this was also vomited. Approximately 21 hours after admission 2 gm. of para-aminobenzoic acid in 10 cc. of 5 per cent sodium bicarbonate solution was given in 60 cc. of grape juice. This was retained and continued to be retained throughout the administration of this medication at 2-hour intervals and at the same dosage for the following 6 days. Additional treatment consisted of a high-protein, high-calorie diet, fluids as tolerated and a preparation high in vitamin content three times a day, with vitamin K injections every other day. Daily white-cell count and differential counts were done, as well as daily urinalysis. Approximately 24 hours after the first successful administration of the para-aminobenzoic acid the temperature had fallen to 99°F. The pulse, which had varied between 120 and 160, fell to 100. Within 48 hours after the administration of para-aminobenzoic acid, the temperature was normal and remained so throughout the patient's stay in the hospital. The blood pressure showed no appreciable change throughout the hospital stay. The white-cell count was 9300 on the 2nd hospital day, 12,300 on the 3rd day and 10,000 on the 4th day, varying between 6700 and 11,000 on the 5th, 6th and 7th days. The neutrophil count remained between 55 and 69 per cent, with 2 to 4 per cent eosinophils on the 5th, 6th and 7th days. Daily urine tests remained negative except for an olive reaction to Benedict's solution on one occasion.

The rash responded in much the same way as when serum is successfully administered. Several areas that were petechial gradually regressed, leaving small brown spots on the skin. The macules gradually faded out and were completely gone within 5 days of entry. Response to the drug was prompt and gratifying. Blood agglutination tests‡ taken 10 days after admission were reported as follows: "Agglutination for *Proteus vulgaris* (strain X19) is positive in a dilution of 1:640, and agglutination for Rocky Mountain spotted fever is positive in a dilution of 1:16; the test for endemic typhus is negative." Bacteriologic examination of the blood on August 19 showed that the complement-fixation test for Rocky Mountain spotted fever was positive in a dilution of 1:64. The test for endemic typhus was negative.

DISCUSSION

Although blood concentrations of para-aminobenzoic acid were not determined, the patient's response to this medication is considered to have been prompt and gratifying. This case responded in the same way as those in which antiserum is successfully used.[5] In our experience there have been no rapid recoveries of the disease when specific measures were not employed early.[6]

SUMMARY

A case of Rocky Mountain spotted fever treated successfully with para-aminobenzoic acid is presented. No toxic effects to the drug were noted.

REFERENCES

1. Snyder, J. C., Maier, J., and Anderson, C. R. Report to the Division of Medical Sciences, National Research Council, dated December 26, 1942.
2. Hamilton, H. L., Plotz, H., and Smadel, J. E. Effect of para-aminobenzoic acid on growth of typhus rickettsiae in yolk sac of infected chick embryo. *Proc. Soc. Exper. Biol. & Med.* **58**:255-262, 1945.
3. Rose, H. M., Duane, R. B., and Fischel, E. E. Treatment of spotted fever with para-aminobenzoic acid. *J. A. M. A.* **129**:1160, 1945.
4. Greeley, D. M. Treatment and prevention of Rocky Mountain spotted fever in children. *M. Clin. North America* **31**:647-658, 1947.
5. Topping, N. H. Rocky Mountain spotted fever. *M. Clin. North America* **27**:722-733, 1943.
6. Rubenstein, A. D., and Rowley, H. F. Endemic Rocky Mountain spotted fever in Massachusetts. *New Eng. J. Med.* **229**:455-461, 1943.

*Chief of medicine, Cape Cod Hospital.
†Formerly, assistant resident, Cape Cod Hospital.

‡Tests performed at the National Institute of Health, Bethesda, Maryland.

MEDICAL PROGRESS

ALLERGY

WALTER S. BURRAGE, M.D.*

BOSTON

THE year 1947 was marked by an ever-increasing number of papers on allergy in the medical literature. These appeared not only in journals devoted to this specialty itself but also in a wide range of other medical and scientific periodicals. This broadening of the scope of allergy has not been confined to the clinical problems of the allergist, the internist, the dermatologist or the pediatrician. It has spread into the realms of pathology, biochemistry, pharmacology, immunology and immunochemistry. Investigators in these basic sciences of medicine have done much to increase the understanding of allergic reactions and to suggest the possible importance of this type of mechanism in diseases other than such commonly recognized allergic disorders as asthma and hay fever. This gradual infiltration into allied fields has helped to extend the horizons of allergy both from a practical and from a potential standpoint. It has also made it necessary for recent reviewers to confine themselves to consideration of but a few aspects of allergy at a time.

The present paper is limited to the following topics of general interest that have shown signs of progress in the field of allergy during the past year: a review of the reviews; modern immunologic and pathological concepts of allergy; histamine and antihistaminic drugs; and emotional factors.

REVIEWS

Recent general reviews have covered many branches of the literature. Kaplan and Ehrlich[1] have dealt with various aspects of hay fever. The subject of respiration has been covered by Brown,[2] with emphasis on several phases of this complicated mechanism, which is important to allergy.

Boyd[3] has reviewed recent developments in the field of immunity from the standpoint of a chemist but with special reference to the interests of the allergist, discussing the interaction of antibodies with antigens or haptens. Kabat[4] points out the immunochemical difficulties involved in the study of the quantitative aspects of this type of human allergic reaction. Cooke,[5] in discussing the immunology of allergy, provides an immunologic classification dividing such reactions into two types: the immediate or wheal-forming type, which may be of either the induced or the spontaneous variety, and the delayed immunologic reaction, which produces an inflammatory response of the tuberculin, the dermatitic or the vascular type. Of general interest is his comment that an antigen-antibody mechanism has not been demonstrated in most of the diseases of the delayed or inflammatory type of reaction. Such a mechanism, however, is usually operative in immediate or wheal-forming disorders, such as serum disease, seasonal hay fever and extrinsic asthma.

Drug allergy has been well reviewed by Dragstedt[6] and by Sherman.[7] The latter emphasizes the point that in cases of allergy due to nonprotein drugs, circulating antibodies are demonstrable only in rare cases.[8] Skin tests, with the exception of patch tests in contact dermatitis, are therefore of no value. In sensitization due to protein drugs or gums, however, circulating antibodies can usually be demonstrated. In such cases, skin tests by the scratch or intradermal methods may be helpful. A further point is not always appreciated. Drug fever, leukocytosis, arthralgia, lymphadenopathy and many types of skin reactions, as well as the usual allergic symptoms, are often due to drug sensitivity. The modus operandi of drug allergy is still under debate but is worth brief consideration. Studies by Landsteiner[9] and others have demonstrated that simple chemical compounds can combine with proteins and act as haptens, thereby determining the specificity of antibody reactions. This theory has helped to correlate crystalloid drug sensitivity with the more familiar protein sensitization. Chase,[10] however, has recently been able to sensitize guinea pigs with repeated intradermal doses of simple chemical compounds dissolved in olive or corn oil. Transfer of serum from such prepared animals to skin sites on normal guinea pigs was successful in sensitizing the latter. When such sites were tested with the original chemical, immediate wheal-forming positive reactions were obtained, often with pseudopods. Chase[11] also succeeded in preventing this sensitization by feeding the same chemical to guinea pigs prior to repeating the experiment described above. These observations are important in that they suggest that drug allergy may operate along the paths of the better known antigen-antibody mechanism. Further observations from the immunologic and biochemical standpoint were made and dis-

*Assistant physician, Massachusetts General Hospital; chief of allergy clinics, Massachusetts General Hospital and Newton-Wellesley Hospital.

cussed by Frazier and Small[12] in their consideration of allergic dermatitis.

Excellent progress reports have appeared within the past year in pediatric allergy by Glaser,[13] miscellaneous allergy by Halpin[14] and dermatologic allergy by Baer and Leider.[15] Stevenson and Alvord,[16] in an analysis of allergy of the nervous system, point out that headache, somnolence and convulsions, as well as signs of focal or general disease of the central or peripheral nervous system, may be produced by hypersensitivity. Rackemann,[17] in a scholarly review of the 1946–1947 literature of allergy has discussed many basic and controversial concepts and has summarized several lines of progress. Unger and Gordon[18] have presented a critical review of the domestic and foreign literature on asthma for the same period.

Pathology

The recognition of characteristic histologic changes in various types of allergic disease is recent and one of the more interesting if not the most clinically valuable advance in allergy. According to Bohrod's[19] classification, the results of tissue injury may be anaphylactoid, necrotizing or granulomatous, depending upon various factors, which include the strength of the inflammatory stimulus, the responsiveness of the host and the velocity and the duration of the reaction. The histologic picture varies with the type of lesion. The simplest form of the immediate wheal-like reaction presents a picture characterized primarily by exudative changes such as edema and swelling of collagen fibrils. The diseases that bring this about comprise the common allergic syndromes seen in practice. The reactions are usually mild in intensity and brief in duration and leave the tissues without permanent damage. The granulomatous lesions, on the other hand, are the result of inflammation and cause more permanent damage. Their essential structure consists of a central area of necrosis surrounded by proliferative reticuloendothelial cells, which often assume a radial, palisaded arrangement. Necrotizing lesions likewise destroy tissue. They are characterized by diffuse necrosis involving parenchymal cells, interstitial tissue and vascular structures.

Rich[20] was a pioneer in such pathological studies. He found lesions resembling those of periarteritis nodosa in patients who had died at Johns Hopkins Hospital of serum sickness following sulfonamide therapy. More recently he[21] has pointed out 32 fatal cases in that hospital with similar diagnoses occurring since the advent of the sulfonamides, in contrast to 6 such deaths during all previous years. Gregory and Rich[22] have produced comparable lesions in animals by the injection of egg albumin, and Selye[23] by inoculation of hormone extracts and later by exposure to cold.[24] From the diversity of stimuli that can produce characteristic lesions similar to those found in diseases known to be allergic, it seems evident that an antigen-antibody mechanism is not always essential. Furthermore, similar types of histologic lesions have been described in diseases not considered to have more than a bowing acquaintance with clinical allergy. Among these are disseminated lupus erythematosus, scleroderma, dermatomyositis, Loeffler's syndrome, rheumatic fever and rheumatoid arthritis. Klemperer,[25] in a recent review of this subject, agrees that whereas certain pathologic lesions characterized by collagen swelling and vascular damage are highly characteristic and their presence suggests allergy as a possible cause, they are not specific for the allergic response and are therefore not of diagnostic clinical value.

Periarteritis nodosa has stimulated interest not only from the pathological but also from the clinical standpoint. Elkeles[26] emphasizes the conception that this disease may be an extreme degree of vascular allergy and likewise calls attention to the great variety in the clinical picture including fever of the remittent type, tachycardia, polyneuritis, polymyositis, albuminuria, cylindruria, hypertension, blood eosinophilia and asthmatic attacks with bronchitis. Contratto[27] described 2 cases, 1 in a man with active pulmonary tuberculosis in whom, at different times, biopsies of the lymph nodes showed first periarteritis and later tuberculosis. Bergstrand[28] accents the morphologic similarity between periarteritis nodosa and the transitory infiltration of the lungs in Loeffler's syndrome. Two cases of this disease are presented by Alpher[29]; ragweed-pollen sensitivity was considered to be the etiologic factor in 1. The other, in an asthmatic patient, was characterized by two successive and recent attacks and one probable attack four years previously. Henderson and Pierce[30] have stressed the transitory nature of the focal pulmonary lesions in this disease as demonstrated by serial x-ray films. Tropical eosinophilia falls in the same group. It is important that this disease may be relieved, as in Irwin's[31] 2 cases, by treatment with arsenicals.

Histamine and Antihistaminic Drugs

The greatest clinical advance in allergy in recent years has been provided by the antihistaminic drugs. Their development is an outgrowth of inquiries into the role of histamine in allergy. These studies were initiated in 1910 by Dale and Laidlaw,[32] who noted the similarity of the action of histamine and the manifestations of anaphylactic shock in animals. On the basis of the histamine theory, various efforts have been made within the past decade to counteract the effects of this drug. The first of these was by attempted desensitization with repeated injections of histamine. This was followed by a wide use of histamine azoprotein "hapamine" with the hope that a conjugate might stimulate antibodies more easily than treatment with histamine itself. Histaminase was next offered

as a possible means of destroying histamine, but this enzyme failed in vivo to live up to its promises in vitro. None of these methods of treatment have been accepted with more than limited enthusiasm. The antihistaminic drugs provide a different approach to the problem; they have a competitive chemical action against histamine. Loew,[33, 34] in reviews of the pharmacology of these compounds, states that their effectiveness appears to be definitely related to their ability to diminish or block the effects of histamine upon vascular and visceral smooth muscle and permeability of capillaries. He concludes that none of the evidence suggests that these drugs influence the antigen-antibody reaction.

Rose[35] postulates that patients with allergic diseases demonstrating histamine effects must have two operative factors. The first is that the tissues must be hypersensitive to histamine, and the second that there must be a shift of this substance from the intracellular or inactive form to the extracellular or free state and that small amounts of histamine may thus be continually released, producing local effects, and then rapidly removed from the blood by means of the kidneys.

Feinberg and his associates[36–42] have been pioneers in reviewing the experimental and therapeutic status of the antihistaminic drugs. Reports of clinical results with the most widely known of these medications, benadryl and pyribenzamine, have now been recorded in several thousand cases. Such accounts include the percentage effectiveness of either or both drugs in various conditions, their comparative merits and the frequency of their side reactions. Carefully controlled series of over 100 cases in each study have been published by Feinberg et al., Henderson and Rose,[43] Blumenthal and Rosenberg,[44] Wagner,[45] Arbesman and his co-workers,[46, 47] the American Academy of Allergy,[48] Loveless and Brown,[49] Waldbott,[50] O'Leary and Farber,[51] Levin[52] and Todd.[53]

Loveless,[54] in a recent comparative study based upon a survey of twenty-six clinical reports from the literature, summarizes the results of trials in over 2000 cases with pyribenzamine and in nearly 1500 with benadryl, as well as a percentage tabulation of side reactions (Tables 1 and 2).

It is obvious from these tables and from compilations by other reviewers[17, 36] that benadryl and pyribenzamine provide temporary relief in varying degrees for many types of allergic manifestations. It is equally evident that side reactions are common. These are usually transient in nature and are seldom serious or of more than temporary concern either to the patient or to the physician. Occasionally, however, more serious reactions occur. Epstein[55] reported the development of eruptions in 2 patients with atopic eczema while they were taking pyribenzamine. One eruption was of the eczematoid type; the other resembled pityriasis rosea. Both cleared with the withdrawal of the drug and recurred on its readministration. Blanton and Owens[56] recorded the appearance of agranulocytosis in a seventy-three-year-old woman after eight weeks of therapy for urticaria with pyribenzamine. After withdrawal of the drug and treatment with penicillin, the blood and clinical pictures returned to normal. Urinary incontinence, involuntary spastic movements of the extremities, slurred speech and irrational behavior were noted by Weil[57] in a boy of three and a half after two doses of 50 mg. of Benadryl and a third of 100 mg. six hours later. Sternberg[58] describes a twenty-two-year-old nurse who was hospitalized for hysteria after one week's treatment with daily doses of 200 mg. of benadryl. On withdrawal of the drug she became normal. Geiger, Rosenfield and Hartman[59] reported palpitation, dimmed vision, malaise, drowsiness, heartburn and nausea after a daily total dose of 300 mg. of benadryl given over a three-

TABLE 1. *Disorders Alleviated by Histamine Antagonists, in Order of Their Susceptibility to Benadryl and Pyribenzamine.**

DISORDER	BENADRYL		PYRIBENZAMINE	
	PATIENTS TREATED	PATIENTS IMPROVED	PATIENTS TREATED	PATIENTS IMPROVED
		%		%
Serum disease	3	100	1	100
Overdose reactions	4	100	25	92
Dermographia	6	100	46	83
Allergic rhinitis, extrinsic non-seasonal	6	100	144	72
Urticaria, acute	135	95	250	85
Urticaria, chronic	261	87	266	79
Dermatitis, contact	18	78		
Rhinitis, seasonal (hay fever)	320	77	558	78
Dermatitis, eczematous and miscellaneous	23	74‡	31	45
Physical allergy	7	71	10	70
Ménière's syndrome	13	69‡	5	20
Headache, histamine and other types	14	64	8	50
Rhinitis, intrinsic,† allergic	183	59	399	58
Dermatitis, atopic	76	58	119	61
Asthma, intrinsic,† allergic	210	53‡	294	32
Asthma, seasonal	53	49	42	45
Migraine	38	45	6	17
Asthma, nonseasonal, extrinsic	23	39	70	49
Pruritus	40	20	26	61

*Adapted from Loveless.[54]

†Some of the diagnostic data were inadequate to determine whether the patient belonged to the intrinsic or to the nonseasonal, extrinsic class.

‡Suggested superiority over the other drug.

TABLE 2. *Side Reactions to Benadryl and Pyribenzamine.**

SIDE EFFECT	BENADRYL INCIDENCE	PYRIBENZAMINE INCIDENCE
	%	%
Sedation	43.0	8.5
Disorder of central or peripheral nervous system	10.0	3.0
Gastrointestinal complaints	8.0	9.0
Dizziness or vertigo	7.0	3.0
Numbness of lips and tongue	6.0	1.0
Exhaustion	4.5	2.0
Vascular	3.0	1.0
Muscular pain or inco-ordination	1.5	1.0
Hypersensitiveness	1.0	1.0
Miscellaneous	0.2	0.3
Headache	0.0	2.5

*Adapted from Loveless.[54]

day period. After the next dose of 50 mg., the patient was found unconscious. All symptoms subsided with withdrawal of the drug. With the exception of the unconsciousness, they all recurred when the same dosage of benadryl was administered a week later. The dangers of self-medication are illustrated by Borman,[60] who recounts the case of an eighteen-year-old girl who obtained excellent relief of hay fever and asthma from her first day's treatment with two 50-mg. benadryl capsules. Encouraged to increase her own dose, she took forty capsules (2000 mg.) within the following three days. She became drowsy and irrational but with forced fluids completely recovered within forty-eight hours. It was believed that her judgment may well have been affected by the first two capsules of benadryl.

I recently observed the following case, as yet unreported:

A 25-year-old housewife, referred for study of chronic vasomotor rhinitis, had previously been given 200 mg. of pyribenzamine daily for treatment of persistent nasal obstruction. She was apparently normal in other respects. During the first 10 days of this medication, she obtained relief from the nasal symptoms but became increasingly nervous, sleepy, absent-minded and depressed. She even contemplated suicide. At times she forgot how to cook or how to set the table. She also neglected, now and then, to feed her children or to get her husband's dinner upon his return in the evening. She lost 14 pounds in 10 days. On the 11th evening of medication, her husband entered the kitchen to find the patient finishing the last of a new bottle of twenty-five 50-mg. pyribenzamine tablets purchased that day. Her physician was on vacation, but another doctor was called. He prescribed an emetic, with resultant evacuation of the stomach contents. During the next few days the psychotic symptoms gradually disappeared, and at the end of a week the patient felt perfectly normal except for nasal obstruction, which had recurred. She therefore decided to resume the pyribenzamine in doses of 200 mg. daily. All the former symptoms slowly returned. Five days later, she was visiting one of her children sick in the hospital when the child's physician arrived to find the mother sound asleep at her daughter's bedside. Pyribenzamine was immediately stopped, with a gradual return to normal. With the reappearance of nasal obstruction, a 5-day trial was given to thephorin, one of the newer antihistaminics, which was prescribed in amounts of two tablets daily. This therapy was followed by sustained exhilaration and a feeling as if the patient were walking on air or flying. Reduction of the dose to one tablet did not improve the situation, so that this medication was discontinued, with final disappearance of the untoward symptoms.

The satisfactory clinical response to the earlier antihistaminic drugs such as benadryl and pyribenzamine, as well as the obvious disadvantages of their side actions, has prompted much investigation in an effort to obtain more powerful but less toxic products. The trade names of over thirty such antihistaminic substances are already a matter of record. A number of these are having extensive therapeutic trial. Reports have appeared upon clinical results with neo-antergan,[61] antistine[62] and decapryn.[63] Halpern[64] has been working on the thiodiphenylamine derivatives, of which 3015 RP and 3277 RP are the most promising. This new chemical series is reputed to be less toxic and more active than earlier ones. It is too early to evaluate these or the many other antihistaminic drugs that will appear upon the market within the near future.

As Feinberg,[36] Burrage[65] and others[48] have stressed, the histamine antagonists are valuable adjuncts to the treatment of allergic disease, but they do not immunize the patient, nor is their benefit more than a brief one. It is obvious that their administration is attended by frequent side effects of varying degrees of severity. Not enough time has elapsed to rule out the possibility of more remote toxic effects.

Emotional Factors

In any large group of patients with allergic manifestations the etiologic factors remain obscure in a considerable percentage even at the end of routine allergic studies. Mitchell et al.,[66] bothered by this common observation, analyzed a group of 600 consecutive cases of representative types of allergy. This series was divided into positive skin reactors whose symptoms such as hay fever and extrinsic asthma could be correlated with proved causative factors and non-reactors with perennial vasomotor rhinitis, "intrinsic" asthma and chronic urticaria. Early age of onset was evident in the reactor group in contrast to a late beginning of symptoms in the other. This in itself is not unusual, since many observers, including Rackemann,[67] have pointed out that asthma starting before the age of thirty is a different disease from that which begins after forty. In the nonreactor group, there was a 2:1 predominance of females with symptoms most common in the third, fourth and fifth decades — a time in life in which the authors considered conflict and situational factors to be related to the production and persistence of allergic symptoms. Subsequently, 1129 cases of perennial asthma observed over a ten-year period were classified according to the major etiologic factors. It was found that 1 out of every 5 of these cases (22.7 per cent) were diagnostic and therapeutic failures. One hundred such year-round cases were next selected for careful individual review, and it was again discovered that approximately the same number (21 per cent) showed signs of psychologic maladjustment in view of the expressions of confusion, hostility, fear, guilt and so forth that were brought out in prolonged and careful history taking. These characteristics were in sharp contrast to the clear-cut, succinct, unemotional statements common in the reactor groups. Gliebe and Kerr[68] presented 4 such cases in detail, illustrating the importance of psychogenic elements in 1 case of chronic headache, in 1 of chronic urticaria and in 2 of primarily intrinsic asthma. They agreed with the previous authors that the role of the emotions in causing, precipitating and aggravating latent allergic sensitization will be adequately recognized and that the study, diagnosis, treatment and relief of allergic manifestations will be substantially furthered if

history taking is broadened to include psychologic events, particularly if these events are correlated with the somatic reactions at the time of occurrence. Mitchell and Curran[69] have reviewed the earlier literature and stressed again the advisability of the sensitive, nondirect method of approach to this type of patient rather than one of abrupt questioning. This technic has seemed in numerous cases to reveal useful psychologic data, with the production of a state of release and attendant psychologic adjustment and symptomatic improvement.

Henderson[70] believes that asthma should be conceived of primarily as an organic disease based on disturbed respiratory physiology — the result of allergic influences — in which psychic and emotional factors may indeed be important in precipitating, modifying or inhibiting attacks in patients already the subjects of asthma. Billings[71] discusses 12 patients with bronchial asthma from the psychogenic standpoint. He warns that the establishment of such an etiology requires relatively long psychotherapeutic guidance and that the more diffuse the complaints, the less satisfactory the therapeutic results are likely to be. Cormia[72] has classified the psychosomatic dermatoses, including such disorders of allergic interest as urticaria, dermographism, pruritus and atopic and contact dermatitis. He outlines a combined dermatologic and psychiatric approach, which he believes lends itself well to all but the more longstanding recalcitrant conditions for which prolonged psychoanalysis is indicated. Metzger[73] recognizes the importance of the emotions and discusses a case. Fabricant[74] deliberately induced fright and emotional upsets in 3 susceptible subjects during determination of the nasal reaction, with a resultant rapid shift from slightly acid (pH 6.5) to alkaline (pH 7.3). A similar type of observation was made by Wolff,[75] who noted vasoconstriction of the nasal mucous membranes of a boy when he was frightened. Nasal congestion appeared, however, when fear disappeared and rage took its place. MacLean,[76] and Swanton,[77] both in Australia, have presented cases to illustrate the psychophysical interreactions in the asthmatic patient. Although Salter[78] emphasized the importance of the psychogenic factor in asthma almost seventy years ago and many observers are now willing to agree to its possible role in allergy, comparatively few papers have appeared upon the subject up to recent years, and even fewer large series of cases have been carefully studied from this angle. I believe that in no case should psychologic study replace but rather that it should more frequently supplement other generally accepted methods of allergic investigation. I predict, moreover, that there will be a wider acceptance of the importance of this approach in certain types of allergic disease.

Conclusions

The field of allergy has now become so broad that its concepts must be integrated with those of the fundamental medical sciences as well as with those of its parent internal medicine. The skin test has ceased to be the only trade-mark of the allergist. Advances in allergy are often initiated, developed and reported in other fields. Progress in allergy can no longer be reviewed in its entirety.

The modern role of pathology in allergy is illustrative of this modern trend. Recent pathological studies suggest a common histologic denominator between diseases now known to be allergic and several conditions with similar histology but with no clinical characteristics of allergy. Future investigations may point the way to some common causative mechanism in these diseases.

A review of the antihistaminic drugs records a definite advance in allergic therapy. Caution is advised that their administration be carefully supervised, and it is recommended that they be employed to supplement rather than to replace well tried principles of allergic management.

The psychologic approach to the etiology of otherwise unexplained allergic disease marks another step forward. A broader acceptance of this diagnostic and therapeutic aid to allergy is urged and predicted for the future.

References

1. Kaplan, M. A., and Ehrlich, N. J. Progress in allergy: review of literature of 1946. *Ann. Allergy* 5:253-273, 1947.
2. Brown, E. A. Progress in allergy: respiration: review of recent literature. *Ann. Allergy* 5:381-391, 1947.
3. Boyd, W. C. Immunochemistry: review intended especially for students of allergy. *J. Allergy* 18:125-145, 1947.
4. Kabat, E. A. Quantitative immunochemical aspects of some allergic reactions. *Am. J. Med.* 3:535-544, 1947.
5. Cooke, R. A. Immunology of allergic disease. *Am. J. Med.* 3:523-534, 1947.
6. Dragstedt, C. A. Idiosyncrasy to drugs. *J. A. M. A.* 135:133-136, 1947.
7. Sherman, W. B. Drug allergy. *Am. J. Med.* 3:586-600, 1947.
8. Sherman, W. B., and Cooke, R. A. Sulfadiazine sensitivity with demonstrable skin-sensitizing antibody in serum. *Am. J. Med.* 2: 588-593, 1947.
9. Landsteiner, K. Serological and allergic reactions with simple chemical compounds. *New Eng. J. Med.* 215:1199-1204, 1936.
10. Chase, M. W. Studies in sensitization of animals with simple chemical compounds: antibodies inducing immediate-type skin reactions. *J. Exper. Med.* 86:489-514, 1947.
11. *Idem.* Inhibition of experimental drug allergy by prior feeding of sensitizing agent. *Proc. Soc. Exper. Biol. & Med.* 61:257-259, 1946.
12. Frazier, C. N., and Small, A. A. Allergic dermatitis: view of its immunologic and biochemical implications. *Am. J. Med.* 3:571-585, 1947.
13. Glaser, J. Progress in allergy: pediatric allergy: critical review of recent literature. *Ann. Allergy* 5:60-88, 1947.
14. Halpin, L. J. Progress in allergy: miscellaneous allergy. *Ann. Allergy* 5:166-186, 1947.
15. Baer, R. L., and Leider, M. Progress in allergy: dermatologic allergy. *Ann. Allergy* 5:578-593, 1947.
16. Stevenson, L. D., and Alvord, E. C., Jr. Allergy in nervous system: review of literature. *Am. J. Med.* 3:614-620, 1947.
17. Rackemann, F. M. Allergy, review of literature of 1946 and 1947. *Arch. Int. Med.* (in press).
18. Unger, L., and Gordon, B. F. Progress in allergy: bronchial asthma (IV): critical review of literature. *Ann. Allergy* 6:64-93, 1948.
19. Bohrod, M. G. Classification of histologic reactions in allergic diseases. *Am. J. Med.* 3:511-522, 1947.
20. Rich, A. R. Role of hypersensitivity in periarteritis nodosa as indicated by seven cases developing during serum sickness and sulfonamide therapy. *Bull. Johns Hopkins Hosp.* 71:123-140, 1942.

21. *Idem.* Hypersensitivity in pathogenesis of diseases characterized by collagens and vascular damage. *J. Allergy* (in press).
22. Gregory, J. E., and Rich, A. R. Experimental production of anaphylactic pulmonary lesions with basic characteristics of rheumatic pneumonitis. *Bull. Johns Hopkins Hosp.* **78**:1-12, 1946.
23. Selye, H. General adaptation syndrome and diseases of adaptation. *J. Clin. Endocrinol.* **6**:117-230, 1946.
24. *Idem.* General adaptation syndrome and diseases of adaptation. *J. Allergy* **17**:231, 289 and 358, 1946.
25. Klemperer, P. Pathologic anatomic aspects of allergy. In Cooke, R. A. *Allergy in Theory and Practice.* 572 pp. Philadelphia: W. B. Saunders Co., 1947. P. 69.
26. Elkeles, A. Periarteritis nodosa. *Brit. M. J.* **1**:738, 1947.
27. Contratto, A. W. Periarteritis nodosa: report of two cases, one with special reference to sensitivity factors. *Arch. Int. Med.* **80**:567-578, 1947.
28. Bergstrand, H. Morphological equivalents in polyarthritis rheumatica, periarteritis nodosa, transient eosinophilic infiltration of lung and other allergic syndromes. *J. Path. & Bact.* **58**:399-409, 1946.
29. Alpher, I. M. Loeffler's syndrome: report of two cases, one with recurrent features, and one associated with hay fever. *J. Allergy* **18**:39-46, 1947.
30. Henderson, A. T., and Pierce, C. B. Transitory focal pulmonary edema and eosinophilia (Loeffler's syndrome). *Am. J. Roentgenol.* **58**:391-406, 1947.
31. Irwin, J. W. Tropical eosinophilia. *Ann. Int. Med.* **25**:329-339, 1946.
32. Dale, H. H., and Laidlaw, P. P. Physiological action of β-iminazolylethylamine. *J. Physiol.* **41**:318-344, 1910.
33. Loew, E. R. Pharmacology of antihistamine compounds. *Physiol. Rev.* **27**:542-573, 1947.
34. Sherrod, T. R., Loew, E. R., and Schloemer, H. F. Pharmacological properties of antihistamine drugs, benadryl, pyribenzamine and neoantergan. *J. Pharmacol. & Exper. Therap.* **89**:247-255, 1947.
35. Rose, B. Rôle of histamine in anaphylaxis and allergy. *Am. J. Med.* **3**:545-559, 1947.
36. Feinberg, S. E. Histamine and antihistaminic agents: their experimental and therapeutic status. *J. A. M. A.* **132**:702-713, 1946.
37. Friedlaender, S., Feinberg, S. M., and Feinberg, A. R. Histamine antagonists. VI. Comparative antihistaminic activity of some ethylenediamine drugs in guinea pig. *J. Lab. & Clin. Med.* **32**: 47-50, 1947.
38. Bernstein, T. B., Rose, J. J., and Feinberg, S. M. New antihistaminic drugs (benadryl, pyribenzamine and neoantergan) in hay fever and other allergic conditions. *Illinois M. J.* **92**:90-95, 1947.
39. Rose, J. M., Feinberg, A. R., Friedlaender, S., and Feinberg, S. M. Histamine antagonists: comparative antianaphylactic activity of some new antihistaminic drugs. *J. Allergy* **18**:149-155, 1947.
40. Feinberg, S., and Friedlaender, S. Histamine antagonists. IV. Pyribenzamine in symptomatic treatment of allergic manifestations. *Am. J. M. Sc.* **213**:58-60, 1947.
41. Rose, J. M., Feinberg, A. R., Friedlaender, S., and Feinberg, S. M. Histamine antagonists. VII. Comparative antianaphylactic activity of some new antihistaminic drugs. *J. Allergy* **18**:149-155, 1947.
42. Friedlaender, S., and Feinberg, S. M. Histamine antagonists. III. Effect of oral and local use of benzhydryl ether hydrochloride on whealing due to histamine antigen-antibody reactions and other whealing mechanisms: therapeutic results in allergic manifestations. *J. Allergy* **17**:129-141, 1946.
43. Henderson, A. T., and Rose, B. Pyribenzamine (n-pyridyl, n-benzyl, dimethyl-ethylene-diamine-hydrochloride) in treatment of allergy. *Canad. M. A. J.* **57**:136-140, 1947.
44. Blumenthal, L. H., and Rosenberg, M. H. Diphenhydramine hydrochloride ("benadryl hydrochloride"): report on its use in one hundred and thirty-seven patients. *J. A. M. A.* **135**:20-25, 1947.
45. Wagner, H. C. Use of new antihistaminic substances in treatment of allergic disorders. *M. Clin. North America* **31**:43-51, 1947.
46. Arbesman, C. E., Koepf, G. F., and Lenzner, A. R. Clinical studies with n'benzyl, dimethylenediamine monochloride (pyribenzamine). *J. Allergy* **17**:275-283, 1946.
47. Arbesman, C. E., Cohen, V. L., and Osgood, H. Pyribenzamine versus specific hyposensitization in treatment of pollinosis: comparative study. *J. Allergy* **18**:311-324, 1947.
48. Chobot, R. Report of clinical studies on use of pyribenzamine in allergic diseases by Committee on Pharmaceuticals and Medicaments of American Academy of Allergy. *J. Allergy* **17**:325, 1946.
49. Loveless, M. H., and Brown, H. Comparison between clinical effects of pyribenzamine and those of benadryl. *New Eng. J. Med.* **237**: 501-504, 1947.
50. Waldbott, G. L. Clinical results with benadryl. *J. Allergy* **17**:142-144, 1946.
51. O'Leary, P. A., and Farber, E. M. Benadryl in treatment of certain diseases of skin. *J. A. M. A.* **134**:1010-1013, 1947.
52. Levin, S. J. β-dimethylaminoethyl benzhydryl ether hydrochloride (benadryl): its use in allergic diseases. *J. Allergy* **17**:145-150, 1946.
53. Todd, L. C. Some clinical observations on use of benadryl for symptomatic relief of allergic conditions: report of 188 cases. *Ann. Allergy* **4**:282-287, 1946.
54. Loveless, M. H. Therapeutic and side effects of pyribenzamine and benadryl: comparative study based upon survey of twenty-six clinical reports in literature. *Am. J. Med.* **3**:296-308, 1947.
55. Epstein, E. Dermatitis occurring during therapy with tripelennamine hydrochloride ("pyribenzamine hydrochloride"). *J. A. M. A.* **134**:782, 1947.
56. Blanton, W. B., and Owens, M. E. B., Jr. Granulocytopenia due probably to "pyribenzamine." *J. A. M. A.* **134**:454, 1947.
57. Weil, H. R. Unusual side effect from benadryl. *J. A. M. A.* **133**: 393, 1947.
58. Sternberg, L. Unusual side reaction of hysteria from benadryl. *J. Allergy* **18**:417, 1947.
59. Geiger, J., Rosenfield, S. Z., and Hartman, D. L. Unusual reaction following benadryl administration. *J. A. M. A.* **133**:392, 1947.
60. Borman, M. C. Danger with benadryl of self medication and large dosage. *J. A. M. A.* **133**:394, 1947.
61. Bernstein, T. B., Rose, J. M., and Feinberg, S. M. New antihistaminic drugs (benadryl, pyribenzamine and neoantergan) in hay fever and other allergic conditions. *Illinois M. J.* **92**:90-95, 1947.
62. Friedlaender, A. S., and Friedlaender, S. Evaluation of antistine, new antihistaminic substance. *Ann. Allergy* **6**:23-29, 1948.
63. Brown, E. A., Weiss, R., and Maher, J. P. Clinical evaluation of new histamine antagonist "decapryn." *Ann. Allergy* **6**:1-6, 1948.
64. Halpern, B. N. Experimental research on new series of chemical substances with powerful antihistaminic activity: thiodiphenylamine derivatives. *J. Allergy* **18**:263-272, 1947.
65. Burrage, W. S. Recent therapeutic trends in allergy. *New Eng. J. Med.* **238**:181-184, 1948.
66. Mitchell, J. H., Curran, C. A., Mitchell, W. F., Swan, I., and Myers, R. Personality factors in "allergic" disorders. *J. Allergy* **18**:337-340, 1947.
67. Rackemann, F. M. Working classification of asthma. *Am. J. Med.* **3**: 601-606, 1947.
68. Gliebe, P. A., and Kerr, W. J. Recognition of emotional factors in allergic manifestations. *Am. J. Med.* **3**:607-613, 1947.
69. Mitchell, J. H., and Curran, C. A. Some psychosomatic aspects of allergic diseases. *Psychosom. Med.* **9**:184-191, 1947.
70. Henderson, A. T. Psychogenic factors in bronchial asthma. *Canad. M. A. J.* **55**:106-111, 1946.
71. Billings, E. G. Dynamic and therapeutic features of seventeen cases of so-called psychogenic asthma. *Rocky Mountain M. J.* **44**:197-199, 1947.
72. Cormia, F. E. Psychosomatic factors in dermatoses: critical analysis of diagnostic methods of approach. *Arch. Dermat. Syph.* **55**:601-620, 1947.
73. Metzger, F. C. Emotions in allergic individual. *Am. J. Psychiat.* **103**:697-699, 1947.
74. Fabricant, N. D. Effect of emotions on hydrogen ion concentration of nasal secretion in situ, with comment on terminology of nasal hydrogen ion concentration measurement. *Arch. Otolaryng.* **43**: 402-408, 1946.
75. Wolff, H. A. Life situations, emotions, and nasal functions: report on research. Read before American Society for Research in Psychosomatic Problems, New York City, February, 1946.
76. MacLean, R. E. G. Asthma and some psychophysical interrelations. *M. J. Australia* **1**:287, 1947.
77. Swanton, C. Asthma and other psycho-physical interrelations. *M. J. Australia* **1**:138-145, 1947.
78. Salter, H. H. *On Asthma: Its pathology and treatment.* 284 pp. New York: William Wood & Co., 1882.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

BENJAMIN CASTLEMAN, M.D., *Associate Editor*

EDITH E. PARRIS, *Assistant Editor*

CASE 34221

PRESENTATION OF CASE

A sixty-two-year-old electrician entered the hospital complaining of malaise and exhaustion.

Five days before admission he noted abdominal rumbling and loose stools. He felt that he was about to have an attack of diarrhea. He went to the basement in the dark to take a drink of whisky to relieve this and by mistake picked up a bottle of carbon tetrachloride and drank about an ounce. As soon as he tasted it he spat it out and induced vomiting with his finger. He vomited numerous times during the following several hours and also had repeated watery stools. Later that evening he felt better although somewhat weak. He slept well but on the following morning was so weak that he stayed home from work. During the following two days he continued to have severe anorexia, taking very little food or drink. In addition, he noted an intermittent, dull, aching pain in the lower back, "between the hips," and soreness in the right upper quadrant. His wife noticed that his eyes were bloodshot and the surrounding tissues swollen. The urinary output decreased to little more than a few drops each day. During the twenty-four hours preceding entry all symptoms seemed to decrease in severity. He felt somewhat stronger, and the pain in the back diminished. He passed about an ounce of normal-looking urine during this twenty-four-hour period. There had been no jaundice, chills, fever or hematuria.

The past history revealed an attack of acute nephritis at the age of twenty-two, necessitating eight weeks of convalescence at home. There had apparently been no residua. There was no known albuminuria or hypertension. The patient denied excessive alcoholic intake.

Physical examination revealed a well developed, slightly obese, restless man in no acute distress. There was a peculiar odor to the breath, which was described as being neither characteristically uremic nor mousy. The periorbital tissues and conjunctivas were edematous and hemorrhagic. The optic fundi were not remarkable. There was no icterus of the skin or scleras. The lungs were clear, and the heart was of normal size without murmurs. The liver edge, which was smooth, soft and moderately tender, was palpated two or three fingerbreadths below the costal margin. There was percussion tenderness over both costovertebral angles. The extremities were normal.

The temperature was 98.6°F., the pulse 80, and the respirations 25. The blood pressure was 165 systolic, 90 diastolic.

The urine was cloudy and gave a ++++ test for albumin; the specific gravity on two specimens was 1.010. The sediment contained 20 to 30 white cells and 15 to 20 red cells per high-power field. In addition, 6 to 8 epithelial cells, loaded with fat droplets, and occasionally large granular casts were seen. The red-cell count was 4,320,000, and the white-cell count 8700, with 72 per cent neutrophils. A stool was negative for occult blood. The nonprotein nitrogen was 250 mg. per 100 cc. The prothrombin time was 27 seconds (normal, 15 seconds).

The patient seemed to do fairly well in spite of the fact that he voided only 75 cc. of urine during the first hospital day. During the second and third days his condition deteriorated, and he gradually became drowsy. Though he passed 360 cc. of urine on the third day, the urinary output dropped again on the fourth to 240 cc. Moist rales developed at the right base. On the fifth day there was an acute onset of severe dyspnea, restlessness and disorientation, which continued for two hours. Finally convulsive and twitching movements of the trunk and extremities appeared, and the patient died.

DIFFERENTIAL DIAGNOSIS

DR. JOSEPH C. AUB: "He went to the basement in the dark to take a drink of whisky and by mistake picked up a bottle of carbon tetrachloride and drank about an ounce." It is a source of wonder to me that it is stated that this man was not an alcoholic even though he went to the dark cellar to get a drink of whisky and drank a whole ounce of carbon tetrachloride before he tasted it.

DR. WILLIAM W. BECKMAN: The patient took whisky for medicinal purposes whenever he was ill; he kept the bottle in the basement.

DR. AUB: I suspect that he often anticipated that he was going to have diarrhea.

The soreness in the right upper quadrant is important. Carbon tetrachloride affects the kidneys and liver, and yet that is the only note in relation to the liver soreness.

This case is typical of death from carbon tetrachloride poisoning. There is no use considering anything else. In my opinion this man died of carbon tetrachloride poisoning. Why on the tenth day, I do not know. There are cases in the literature in which the patient died on the tenth day, and this is earlier than death occurring from bichloride of mercury. The difference, I suppose, lies in the fact that carbon

tetrachloride poisoning involves the liver as well as the kidneys. Though there is very little evidence that the liver was involved in this case, one should be very suspicious of it. There are not an enormous number of deaths from carbon tetrachloride poisoning recorded in the literature. Carbon tetrachloride is not a very hazardous industrial solvent. It can be breathed in fairly high concentration without damage because most of it comes out by the lungs. Many of the deaths are due to swallowing of the poison. They follow the use of carbon tetrachloride as an anthelminthic in doses of 2 or 3 or at most 4 cc. As a result of such medication a fair amount of jaundice develops, with acute yellow atrophy and death. Such a course has occurred in people who are alcoholics or who drink alcohol with the carbon tetrachloride, and in people who take a good deal of fat, the fat escorting the carbon tetrachloride across the intestinal tract. There are a sufficient number of deaths from carbon tetrachloride to cause it to be avoided as a drug. The deaths that occur are characteristic of that in the case under discussion, except that most of the patients have had jaundice. This patient did not have jaundice. Anne Minot,* who worked with us on lead poisoning, found that lethal doses did not kill a dog if calcium gluconate was given intravenously. Calcium and glucose relieve the strain on the liver sufficiently so that the animal did not die when this was given. Most of the animals that did die in her series died from bleeding in the gastrointestinal tract. This patient had no evidence of bleeding, but the dogs in the experiments died of hemorrhage, through either acute ulceration or duodenal ulcer. Carbon tetrachloride causes injury to both the liver and the kidney. The liver is affected mostly at the inside center of the lobule, the outside of the lobule being less involved. This patient showed an enlarged liver and an elevated prothrombin time, but no jaundice. Is autopsy going to show any abnormality? In spite of the fact that he said that he went to the cellar because he did not feel well, he probably consumed a fair amount of alcohol, and I guess that the carbon tetrachloride did him more damage because of the alcoholic habits. On the basis of that, I think that he had a moderate amount of cirrhosis and a moderate amount of acute yellow atrophy. There is no good evidence for such a statement except that he had an enormously high nonprotein nitrogen. I should like to know what the amino acid content of the plasma was. I assume that the determination was not made.

Dr. Beckman: No; it was not.

Dr. Aub: If the patient had acute yellow atrophy, the best evidence would have been elevation of amino acids in the blood stream as well as jaundice. Without those data one cannot make the diagnosis of acute yellow atrophy. On the basis of pain in the right upper quadrant and the large liver, and since carbon tetrachloride usually affects the liver, I shall say that he had a certain amount of liver destruction and acute yellow atrophy, not enough to give jaundice, and that it did not cause his death.

The chief cause of death was injury to the kidneys, which had been previously damaged. Not infrequently carbon tetrachloride affects the kidney as well as the liver; therefore, I expect to find damage to the tubules, severe damage, with acute nephritis, with uremia, convulsions and death. Some edema was probably found in the lungs, particularly the right lower base, which was said to have rales due to the fact, although the record does not say so, that he was given much intravenous saline solution and got rid of very little of it by the kidney. I do not believe that caused the edema in the lungs, but it added to it. He died of uremia and, therefore, had convulsions. Why these patients get convulsions previous to death, I do not know. All the cases that I have seen as well as those in the literature have shown that. I think that is probably a uremic manifestation. Carbon tetrachloride goes wherever there is fat, and yet there is very little present in the central nervous system. Fatty cells in the kidney are not unusual, because, since the drug is a fat solvent, fat gets free, and the plasma is very apt to be lipemic in this condition. It is one of the ways of knowing whether the carbon tetrachloride is doing damage.

Therapy is not usually discussed at these meetings. I think that most people do not pay enough attention to Anne Minot's suggestion of injection of calcium salts for the liver damage of carbon tetrachloride poisoning. Any patient who has acute yellow atrophy ought to be given calcium and also ought to have glucose, which is very saving of the liver in liver damage. These patients also sustain severe kidney damage. If they survive, they show a surprisingly small residue of kidney damage. The only way I know of saving them is by flooding them with fluid (a course that I suppose was followed in the case under discussion) and also by giving them an adequate amount of alkali to produce diuresis. I am glad that there is no time for further discussion because a number of people would disagree with me. But in my experience, with toxic injury to the kidney, patients do well if large quantities of alkalies are given to produce diuresis. I have seen a number of patients with bichloride poisoning who finally urinated when given large amounts of sodium bicarbonate in intravenous injections. If these people can urinate and get over the uremia, a number of them recover with surprisingly small deleterious effect on the kidneys.

Dr. Tracy B. Mallory: Dr. Aub has made the diagnosis seem obvious. Has anyone any questions, or does anyone take exception to that diagnosis?

Mr. William Kiyasu: What is the antidote for carbon tetrachloride poisoning — lavage?

*Minot, A. S. Mechanism of hypoglycemia produced by guanidine and carbon tetrachloride poisoning and its relief by calcium medication. *J. Pharmacol. & Exper. Therap.* **43**:295–313, 1931.

Dr. Aub: After the drug has been swallowed, I suppose so. It is absorbed very rapidly, being a lipid solvent. I suppose that a stomach wash is indicated, but that does not help much unless done very promptly. Even after repeated vomiting, enough of the drug may still be retained to do damage. In bichloride of mercury, for instance, enough will be retained even after the patient has vomited continuously for an hour. I think the stomach should be washed, but castor oil or alcohol, which might further help the absorption, should not be given.

Dr. Beckman: All I can say is that this emphasizes the value of these exercises, because when I had this patient on the ward as nearly as I could tell he had swallowed no carbon tetrachloride at all, but I am obliged now to admit that he must have. I stood out against the whole field, including the patient, on the diagnosis of carbon tetrachloride poisoning.

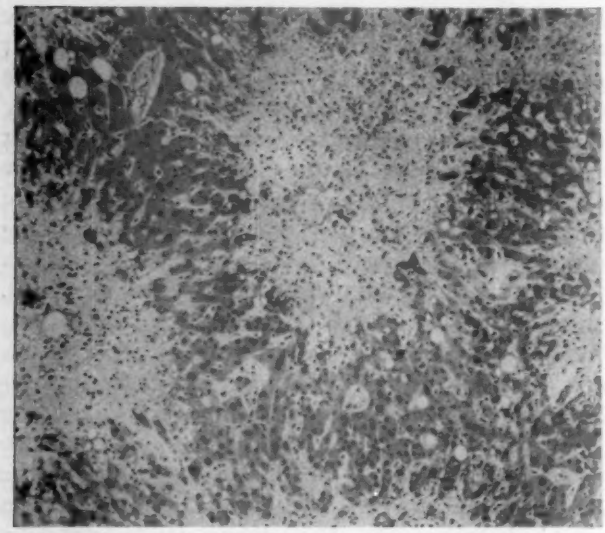

Figure 1.

I thought that it was an exacerbation of the nephritis that he had had forty years previously and that he had developed high blood pressure and severe uremia of which he died. But I think that I was wrong.

Clinical Diagnosis

Acute nephritis.

Dr. Aub's Diagnoses

Carbon tetrachloride poisoning, with renal and hepatic damage.
Uremia.
Pulmonary edema.

Anatomical Diagnoses

Carbon tetrachloride intoxication.
Lower-nephron nephrosis.
Central necrosis of liver, acute.
Pulmonary atelectasis, both lower lobes.
Arteriosclerosis, generalized, moderate.

Pathological Discussion

Dr. Mallory: The autopsy findings to my mind conclusively proved that Dr. Aub was correct. The

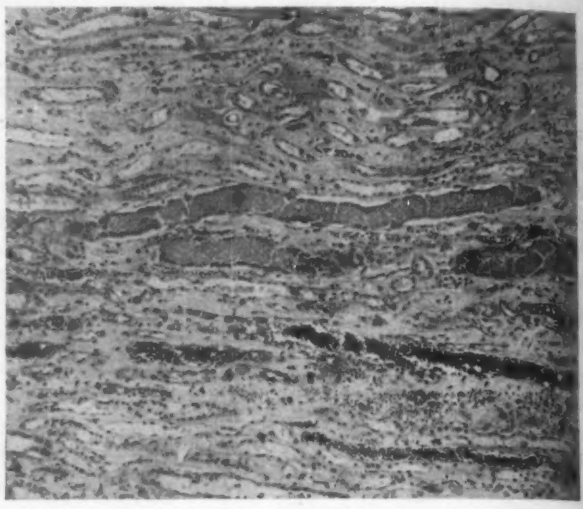

Figure 2.

first view of the liver was almost conclusive, and at post-mortem examination I was struck with the appearance of the liver. It was rather small, and its surface was yellow, with closely sprinkled, bright-

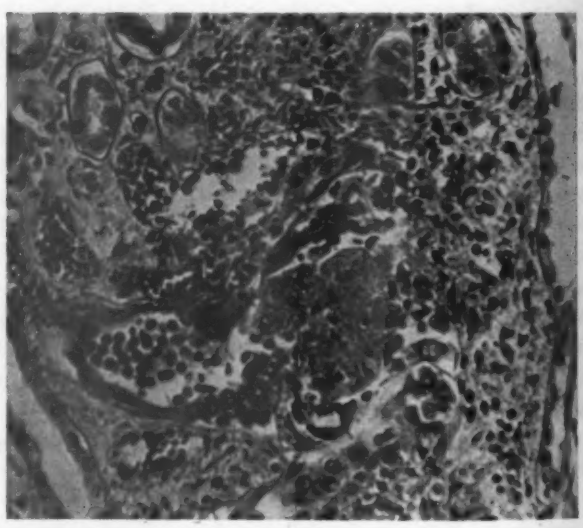

Figure 3.

red dots. On cut surface the central half of every lobule was depressed and red. The microscopical sections showed complete loss of the liver cells in the central half or two thirds of the lobule (Fig. 1). At

the periphery many of the surviving liver cells showed fat vacuoles, another phenomenon characteristic of carbon tetrachloride poisoning. The portal areas, in contrast, were quite normal and showed no cellular infiltration such as one sees in hepatitis.

The kidneys revealed a pigment nephrosis indistinguishable from that of transfusion reaction, which is what one characteristically sees in carbon tetrachloride poisoning. The picture differs from bichloride poisoning, in which the proximal convoluted tubules are injured. Here the straight tubules of the medulla are filled with hemoglobinuric casts (Fig. 2). The cortex showed dilated proximal tubules, but no cellular degeneration, and, incidentally, fat stains of the kidneys did not show any fat. On the other hand, the distal convoluted tubules disclosed a severe grade of degeneration. Figure 3 demonstrates one of the phenomena that we see characteristically in the lower-nephron lesion — a tubule, the wall of which has been destroyed, and there is a cast in process of extension into the stroma, producing a foreign-body type of granuloma in the stroma. The entire picture is like that of a kidney injured by transfusion, crush or sulfonamides. The combination of such a renal lesion with the liver lesion is very unusual in anything except carbon tetrachloride poisoning. In the Army there were a considerable number of cases of this sort that could be surely attributed to carbon tetrachloride injury. Not infrequently the renal symptoms predominated so far over the hepatic symptoms that the latter passed unnoticed.

DR. AUB: If the patient could have weathered the acute illness, what would the end result of the kidney lesion have been?

DR. MALLORY: I believe that there would have been absolute restitution to normal. There are not a great many anatomic observations on record. Kinney observed a case at the Peter Bent Brigham Hospital last year in which the patient died of homologous serum jaundice after three months, having successfully weathered a transfusion reaction in the course of which he had renal insufficiency. That kidney, so far as could be determined anatomically, was normal. There are a fair number of patients who survive a lower-nephron lesion who have been studied functionally. Those kidneys re-establish normal function in approximately two to four months.

CASE 34222

PRESENTATION OF CASE

A fifty-five-year-old Finnish woman entered the hospital because of loss of weight, easy fatigability and the appearance of an abdominal mass, which was gradually increasing in size.

About three months before entry the patient began to lose her appetite and to feel tired. During this period she lost about 25 pounds in weight. Two months before entry she first noticed the appearance of a mass in the abdomen. She claimed that the mass had increased considerably in size since that time. One week prior to admission she began to vomit after the ingestion of any foods or liquids. This had persisted at intervals until entry. The bowel movements had been regular until several days before admission, at which time she had several bouts of nonbloody diarrhea four to six times daily. On the day of entry the bowel movements were normal. She had never had any abdominal pain, and the mass had not been tender.

Thirty-one years before entry she had an operation for a "dropped stomach," and thirteen years previously, while she was in Finland, a hysterectomy was performed. She had two children, aged sixteen and twenty-five years; both were living and well.

The only positive physical finding was the presence of a firm irregular mass (20 by 15 cm.) located mainly in the left midabdomen but extending for a short distance to the right of the midline beneath the umbilicus. The lower border of the mass projected into the pelvis on the left side. It was freely movable and nontender. The abdominal wall was flaccid, and it was possible to pick up the tumor and move it several centimeters in any direction. The greatest motility was from side to side. Pelvic examination revealed no masses in either vault. The uterus was absent. The lower border of the tumor on bimanual examination could be felt at the pelvic brim, more prominently on the left.

The temperature, pulse, and respirations were normal. The blood pressure was 142 systolic, 80 diastolic.

Examination of the blood showed a hemoglobin of 11.8 gm. and a white-cell count of 7800, with 83 per cent neutrophils, 5 per cent lymphocytes, 6 per cent monocytes, 3 per cent eoninophils and 3 per cent basophils. The platelets were normal. The nonprotein nitrogen was 26 mg. per 100 cc.

A barium enema was done on the second hospital day. The colon filled readily without evidence of obstruction. There were numerous small diverticula scattered throughout the sigmoid. A tumor mass was observed in the left side of the abdomen. It compressed the left side of the transverse colon but did not appear to be attached to the colon. The remainder of the colon showed no abnormality. The cecum was freely movable, and the terminal ileum filled readily and appeared normal. The findings were consistent with a mass extrinsic to the large bowel.

On the third hospital day an exploratory laparotomy was performed.

DIFFERENTIAL DIAGNOSIS

DR. MARSHALL K. BARTLETT: In summary, this is the problem of a fifty-three-year-old woman with a three months' history of loss of appetite, weight loss (25 pounds) and a mass in the abdomen of at

least two months' duration, which had increased in size during that time. A week prior to entry she began to have vomiting and intermittent diarrhea. The only helpful physical finding on admission was the presence of a firm, irregular and quite movable mass.

May we see the x-ray films?

Dr. Stanley M. Wyman: These are two films from the barium examination of the colon. The transverse colon is unusually low in position. This film shows compression of the left transverse colon without definite involvement of the mucosa. There is a suggestion of faint outlining of the mass in this position. It lies higher than I thought from the description. Diverticula are present in the sigmoid. The terminal ileum is not well seen. I can see no other masses, and there is no evidence of calcification in this area.

Dr. Bartlett: Can you tell whether it is above or below the transverse colon?

Dr. Wyman: It seems to be above.

Dr. Bartlett: Can you see the kidney shadow and the spleen?

Dr. Wyman: The left kidney shadow can be seen at this point. The lower pole is outlined well. The upper pole cannot be seen. The spleen is outlined and seems to be within normal limits in size and shape. The liver is not remarkable. The right kidney is probably essentially normal.

Dr. Bartlett: That really helps me somewhat, because it rules out certain diseases that I had thought of considering, not having seen the x-ray films and not knowing whether the tumor was above or below the transverse colon. They fairly well rule out the possibility that this was an ovarian cyst, which if present, should have been below the transverse colon. There are various other things against that possibility. I think it would be unlikely that an ovarian cyst would cause nausea and weight loss and gastrointestinal symptoms, unless it was a malignant cyst with extensive metastases, and of course the pelvic examination does not give any hint that this was connected with the pelvic organs. In spite of the fact that a hysterectomy had been performed, the ovaries could have been left behind. We have no information about that. All in all, a cyst of the ovary seems like a remote possibility.

The normal shadow of the spleen, I think, is adequate to rule out the possibility that this was a tumor of the spleen. Such a tumor arising in the spleen would probably displace the colon differently. Again, it hardly is enough to account for the weight loss and gastrointestinal symptoms on that basis. Along the same line of reasoning, I will exclude the kidney although Dr. Wyman is not quite sure about the kidney.

Dr. Wyman: I think that the lower pole is all right.

Dr. Bartlett: That is even more helpful. I shall rule out the possibility of kidney disease. An intravenous pyelogram, of course, would give further evidence on that point, but I take it that the kidney was not seriously considered as the source of this woman's trouble or such an examination would have been done. I dwelt at some length in my mind on that possibility because I had recently been caught at a conference at another hospital on a pelvic tumor that I thought was an ovarian cyst and it proved to be a solitary cyst in an ectopic pelvic kidney.

What other possibilities are there? I thought about the possibility of a lesion in the mesentery of the small bowel, but, again, a tumor in that region would not lie above the transverse colon; it would be below it. I shall dismiss it. Anything that I might say about a cyst or tumor in the mesentery of the small bowel can be equally well applied to the large bowel — to the transverse colon — and we might consider that possibility. There are tumors of the colon that attain considerable size. I am thinking of spindle-cell tumors, which become relatively large without causing much in the way of symptoms. There are two general types based on the point of origin: those that arise in the submucosal areas and the ones that tend to invade the lumen and cause obstruction. I feel sure that one would not attain this size and still give a negative barium enema or a barium enema that shows no evidence of obstruction. The subserous type may get big before symptoms appear. They are apt to manifest themselves by bleeding. We have no particular evidence, other than a moderately reduced hemoglobin, that this patient had bled. There was no history of massive hemorrhage by rectum. No examination of the stool is recorded, but there is nothing particular to suggest that she bled by rectum.

How about a cyst of the mesentery of the transverse colon? I think that is a possibility. Those cysts are rare. When they occur they may either be lymphatic in origin or they may be dermoids. They occasionally can be as big as the mass in this case, but not very frequently. I do not believe that all

these lesions would have been described exactly like this one, which was an irregular, firm mass. I think that a cyst of the mesentery of the transverse colon should be smooth. Again, with a cyst in the mesentery of the bowel or even with a subserous tumor arising from the transverse colon, it is rather difficult to account for the anorexia, the weight loss and the other symptoms.

That brings me down to the pancreas. Was this a lesion arising in the pancreas? In favor of that, it seems to me, is the fact that pancreatic tumors are notorious for insidious onset, with nausea and weight loss, and perhaps this case would be best explained by something of that type. What kind of lesion of the pancreas would resemble this? I think it was too big for a solid tumor of the pancreas. I do not remember seeing or hearing of a solid tumor of this size behaving in this fashion, because they usually produce more symptoms before they reach this size. How about a cyst of the pancreas? There are various types of cysts. The most common is probably the so-called pseudo-cyst, which is the end result of an inflammatory process or sometimes is the result of trauma. These tumors attain good size, and they lie really extrinsic to the pancreas. They start in but extend outside the substance of the pancreas, so that a pseudo-cyst could be in this location and present this picture on physical examination. These cysts, however, are ordinarily unilocular and smooth on the external surface. Likewise, retention cysts, which presumably result from occlusion of some part of the ductile system of the pancreas, are smooth and do not reach this size. If this was a cyst of the pancreas, it seems most likely that it was a cystadenoma. These cysts are multilocular, so that the external surface is irregular, they attain considerable size, often are benign in the early phase and often become malignant as they progress and grow larger. Such a cyst may present in various locations. Above the lesser curvature, between it and the liver, is the most common place. The next most common is between the greater curvature of the stomach and the transverse colon, which is where this tumor seems to have been located. The least common point is below the transverse colon, though the cysts can even be present there. It seems to me, considering the various facts that we have, that a lesion of the pancreas is probably the best diagnosis that I can make. Of the various possible lesions of the pancreas, I think a cystadenoma is probably the most likely.

DR. TRACY B. MALLORY: I am surprised that someone does not try to connect the patient's nationality with the lesion.

DR. BARTLETT: What was her nationality?

DR. MALLORY: Finnish. I knew that we had had an echinococcus cyst not long ago, and as I read over the history, that was my guess; but unfortunately I was not correct.

CLINICAL DIAGNOSIS

Ovarjan tumor ?
Tumor of stomach ?

DR. BARTLETT'S DIAGNOSIS

Cystadenoma of pancreas.

ANATOMICAL DIAGNOSIS

Malignant lymphoma, giant-follicle type, of mesentery of small bowel.

PATHOLOGICAL DISCUSSION

DR. MALLORY: The preoperative diagnosis was probable tumor of the stomach, but I gather that the surgeons were very uncertain about it. The patient was explored. The ovaries and stomach were both found to be perfectly normal. There was a large mass in the root of the mesentery of the small bowel, which had grown outward at one spot along the mesentery to a point where it involved the wall of a short segment of small bowel. The tumor went rather far posteriorly, but the surgeons were able to feel the kidney and were sure that it was not connected with that. The mass as a whole was impossible to resect, but the small segment of involved ileum was resected, since it was feared that the bowel might soon become obstructed. At operation frozen section was attempted, but it was not possible to say what the tumor was; our later section showed it to be malignant lymphoma, giant-follicle type, and the patient is now having x-ray treatment.

The New England
Journal of Medicine

Formerly
The Boston Medical and Surgical Journal

Established 1828

Official Organ of
THE MASSACHUSETTS MEDICAL SOCIETY
and
THE NEW HAMPSHIRE MEDICAL SOCIETY

OWNED BY THE MASSACHUSETTS MEDICAL SOCIETY AND PUBLISHED WEEKLY UNDER THE JURISDICTION OF THE COMMITTEE ON PUBLICATIONS

Richard M. Smith, M.D., *Chairman*
James P. O'Hare, M.D. — Conrad Wesselhoeft, M.D.
Oliver Cope, M.D. — John Fallon, M.D.

Joseph Garland, M.D., EDITOR

ASSOCIATE EDITORS
Thomas H. Lanman, M.D. — Donald Munro, M.D.
Henry Jackson, Jr., M.D.

Clara D. Davies, EXECUTIVE EDITOR
Robert O'Leary, ASSISTANT EDITOR

EDITORIAL BOARD
C. Guy Lane, M.D. — Maxwell Finland, M.D.
Henry R. Viets, M.D. — James M. Faulkner, M.D.
Robert M. Green, M.D. — Carroll B. Larson, M.D.
Dwight O'Hara, M.D. — Francis D. Moore, M.D.
Fletcher H. Colby, M.D. — C. Stuart Welch, M.D.
Robert L. Goodale, M.D. — Vernon P. Williams, M.D.
Chester M. Jones, M.D. — Benjamin Castleman, M.D.
Harvey R. Morrison, M.D. — Hugh R. Leavell, M.D.

SUBSCRIPTION TERMS: $7.00 per year in advance, postage paid, for the United States (medical students, $4.00 per year); Canada, $8.00 per year (Boston funds); $9.50 per year for all foreign countries belonging to the Postal Union.

MATERIAL should be received not later than noon on Thursday, three weeks before date of publication.

THE JOURNAL does not hold itself responsible for statements made by any contributor.

COMMUNICATIONS should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15, Massachusetts. Telephone KE 6-2094.

THE NOLEN–MILES BILL IN RETROSPECT

AFTER much publicity and rather more than the usual amount of misstatement and raucous vituperation from its opponents, the Nolen–Miles Bill has been referred to a legislative research committee for "further study" (*sic*). This is discouraging to those who have worked long and hard for the passage of this sensible piece of legislation. Perhaps the best the medical profession can do is to review the situation and see what can be done in the future.

There are two classes of opponents to this bill. One consists of a rather small minority of sincere but misguided people. To change the opinion of this group seems an impossible task, even though the evidence is overwhelmingly in favor of the value of the bill to humanity and to medical research. If this small group had represented the only opponents there would have been no great difficulty in obtaining favorable action. But there is a much larger and a far more vocal group that advances no reasons against the bill other than those of misguided sentimentality. Unfortunately, this group does not confine itself either to facts or to the real purpose of the bill as explained in its wording. These opponents harp continually on the cruel doctor whose sole interest in the passage of this bill is to steal, torture and eventually kill the pet dog of little Willie Jones. They disregard entirely the present laws for the disposal of lost animals, ignoring the fact that annually thousands of animals are put away in a humane manner because no one claims them at the pounds. It is these animals, which are to be destroyed under the law, that the proponents of the bill wish to make available for the fundamental, important and humane purposes of medical research.

W. E. Mullins, in the *Boston Herald* of March 18, has done an outstanding piece of constructive journalism in his report on the Nolen–Miles Bill. He wrote as follows:

> Legislators have lost sight of the fact that the responsibility is theirs and not that of the medical profession. The politicians should vote on every bill strictly on merit and not on the noise that is made by organized minorities. Busy doctors should not be required to go several times annually to the legislature to plead for the right thing.

One of the legislators had stated in the press, (*Boston Herald*, March 15, 1948) that, "Doctors can individually advise their legislators on bills vital to the protection and progress of Massachusetts medicine — 'or risk losing them.' "

As Mr. Mullins wrote:

> The Massachusetts Medical Society sent its official spokesman to Beacon Hill to plead for it. This is an organization of the foremost medical men of this state. Against the considered opinion of this Society that passage is essential to the continuation of medical research, what do we have? We have this opinion: "I do not think it will help medical science."

The opinion quoted came from a physician serving in the legislature.

The Council of the Massachusetts Medical Society is a body democratically elected by the Society to voice its opinions. At a meeting held

shortly before the bill came to the legislature, the Council voted unanimously to go on record as expressing its hearty approval. What more can a legislator want as evidence of approval of the medical profession? To be sure, a vote is a vote (especially in an election year), but even if every member of the Massachusetts Medical Society appeared individually they would still be greatly outnumbered by the very vocal group of opponents. In addition to the official approval of the Council, however, the Massachusetts Medical Society sent to represent it some of the outstanding physicians and surgeons in the Commonwealth and, indeed, in the country.

The medical profession of Massachusetts made great efforts to obtain favorable action on the bill and came near to success. Disappointing and belittling as it is to be subjected to taunts and insults at a public hearing on Beacon Hill, the medical profession must nevertheless take up this added burden for the greater good of humanity and the advance of the profession. It must accept this challenge and by greater effort make its considered opinion heard, and *effectively* heard by those who, in many cases, are swayed only by the number of votes and not by the thought that goes behind a "yes" or a "no." It must do this rather than adopt a defeatist attitude, which would be welcome to its opponents.

One good, at least, has come out of the clamor of the controversy. A public education process has been started, and the need for greater and continuing education has been made apparent.

MILLIONS FOR DEFENSE

THE Council on National Emergency Medical Service of the American Medical Association sponsored in April a conference to consider the defense of America in the event of a general national emergency. Fifty-one persons were present, representing an impressive majority of the state medical societies as well as a number of national associations of allied professions.

Certain important points were brought out during the course of the conference. Such an emergency, should it occur, will apply especially to our scattered industrial centers, and effective medical service will depend largely on strong state organizations. A resolution was accordingly adopted calling on the component societies of the American Medical Association to activate committees that will work with and under the guidance of the Council.

Such a committee, although it had not yet been activated, had already been authorized by the Council of the Massachusetts Medical Society on October 2, 1946. This action was taken at that time as a logical procedure, with no emotional implications.

Further points were elaborated at the conference in April. In the event of such a national emergency as war with a foreign power, all the available medical personnel of military age should not be called up. Recent history has shown that too many stagnant pools of manpower result from this profligate policy. Another world war would be total to a degree never yet realized, and the ratio of one physician for each fifteen hundred of population, considered sufficient in World War II, would be inadequate for the expected civilian needs. A more flexible deployment of the medical profession to serve both our forces under arms and our population under fire would have to be arranged.

The regular branches of our armed forces should forget their old school ties and give the civilian components equal rank and consideration with their professional military personnel. In past wars it has been a rare honor for a civilian physician, however well equipped, to attain the rank of brigadier general. Furthermore, and this seems almost axiomatic, no emergency should be allowed to disrupt completely the continuity of medical progress and education. The possibility of a national future even after another war should not be entirely disregarded.

Certainly our minds must be kept open for the consideration of wholly new problems in this coldly scientific age. If war should come a new group of special weapons consisting of chemical agents, biologic products and releases of atomic energy with far-reaching effects in both time and space will be available and might be employed. The medical profession will be of transcendent importance in

the event of such a disaster, and none of its value must be canceled out by outworn procedure or by antiquated customs of military regimentation. The chief obligation of civilized man, however, is to prevent, by the most forceful measures that can be undertaken, the catastrophe attendant on the opening of such a Pandora's box. In the contemplation of these weapons we are considering the zenith of military power. In a hypothetical fourth world war, as Einstein has mildly reminded us, man will perhaps revert to rocks as the only available missiles.

A combination of the wisest minds and the strongest hands must guide the future of the world. Their efforts must be directed toward the salvation and not the degradation of mankind. They must prepare for prevention; they must arm to keep the peace. The only fear permissible, as we have been told before, is that of fear itself.

Toynbee has shown that the civilization in control of its own destiny is that in which the creative minority remains actively in quest of moral and not of material gains. Our new, free, western civilization is still of that fiber. Its people are they that "shall mount up with wings as eagles; they shall run and not be weary; and they shall walk and not faint."

VENEREAL-DISEASE CONTROL

A RECENT release from the Office of the Surgeon General reports a remarkable drop in the incidence of venereal disease during 1947.[1] For the Army as a whole, the decrease amounted to 40 per cent; for soldiers stationed in the United States, it was more than 50 per cent. This is an encouraging note in view of the trend toward increased rate in the civilian population as recently reported.[2] The Surgeon General credits this accomplishment to a new approach on the part of the Army, based on "an intelligent appeal to the higher moral sense of the individual," with "moral, spiritual, psychological, as well as objective factors." In this program the reasons for good conduct are stressed through group and individual education and conferences. Programs of activity and planned entertainment help to maintain the interest of the soldier and to steer him away from sources of trouble when he is off duty. This approach has supplanted prior concepts, which emphasized the aspects of prevention, with the implication that the soldier was not remiss so long as his illicit relations did not result in infection. Training films used during the war have been replaced by new films reflecting the current trend, dramatizing "The rewards of good conduct as well as the effect of social diseases on an individual's future health and happiness."

Such a creditable accomplishment is certainly praiseworthy, and it is to be hoped that the rates of venereal disease among civilians will also be reduced. The statistical reports of the United States Public Health Service for the fiscal year 1947 show a rate 2 per cent less in the civilian population of the continental United States than had been predicted.[3] This is still a higher incidence than that of the preceding year. There is usually some degree of parallelism between military and civilian disease, but during periods of peace, the incidence of venereal disease in the general population is not likely to drop so much as the military rate.

A moral and spiritual approach is more likely to be effective in the absence of hostilities. The possibility of impending death that engenders a certain amount of reckless abandon and fatalism is bound to arise in the minds of troops in time of war. This factor complicates the moral aspect of the situation. Nevertheless, an education campaign in time of peace may well lay the foundation for better future success in the control of venereal disease.

REFERENCES

1. *Army Venereal Disease Rate Drops as a Result of New Program.* Release from the Office of the Surgeon-General. Feb. 28, 1947.
2. Diagnosed cases of venereal diseases reported for first time, fiscal years 1941–47. *J. Ven. Dis. Inform.* **28**:102, 1947.
3. Reported civilian venereal disease cases and rates per 100,000 population, continental United States, fiscal year 1947. *J. Ven. Dis. Inform.* **29**:29, 1948.

MASSACHUSETTS MEDICAL SOCIETY

DEATH

ELLIS — Frederick W. Ellis, M.D., of Newton Centre, died on April 30. He was in his ninety-second year.

Dr. Ellis received his degree from Harvard Medical School in 1881. He was a fellow of the American Medical Association and the American Association for the Advancement of Science. He was the last surviving founding member of the American Physiological Society.

A son, Dr. Laurence B. Ellis, of Newton Centre, survives.

A HUNDRED YEARS AGO

Within the circle of benevolent institutions, in this or other countries, there cannot be found a parallel to the one in the City of Boston organized expressly for poor, destitute, sick children. This is truly a charity which is not puffed up and which vaunteth not itself. It seeks no great names upon a circular, to give it importance, carries no contribution box into the church, makes no appeals to the pockets of the benevolently disposed, nor in any way seeks the applause of men. Quietly, without ostentation, without parade, but with a steady purpose, it feeds the hungry, clothes the naked, nurses the sick, and takes care of helpless little children. This is charity indeed, and of which our favored city, aye, and the world may be proud. — Notwithstanding the activity of the press in the United States, the question has been appropriately asked, what is the present state, and what are the future prospects, of the medical literature of this country? There is no dearth of authors. Originality of thought and boldness in execution are characteristics in the practice of American physicians and surgeons. Various institutions vie with each other in developing the resources of a science that investigates the laws of our being, and ameliorates the sufferings to which humanity is incident. New and striking exhibitions of mental effort, in all the various branches of medical study, are being made — and it is morally certain, that a few years will serve to bring out results that will redound to the advancing influence of the medical literature of the Union and place it on a foundation as firm and glorious as the government whose broad mantle covers and protects the whole. — By our exchanges we perceive that the various medical institutions of the country will be generally represented in the approaching meeting of the American Medical Association. The Counsellors of the Medical Society of Massachusetts have appointed *fifty* delegates. At that rate, throughout the country, the number of the whole will be great indeed. — A difficulty has existed in bringing within the embrace of the Massachusetts Medical Society all the well-qualified physicians of the Commonwealth. Some have not liked the payment, it is averred, of an annual tax of three dollars — particularly those who are located so far from the business center of the Society, Boston, as to make it expensive, and not always convenient, to attend; and such, believing that they could not receive an equivalent for their money, in becoming members, have wholly declined all connection. Others, who are excellent, stable-minded, staunch friends, and have exerted themselves to uphold the character of the Society, with veteran determination, have found themselves at times in embarrassment, in not being able to consult with a practitioner who does not belong to the Society — a certain by-law forbidding them to do so. All this has been discussed over and over again in the Council. It is confidently expected that alterations soon to be proposed will meet the cordial concurrence of all parts of the State, and that harmony, prosperity, influence and usefulness will follow their adoption. — Our colleagues in Buffalo, understanding that two Harvard students are at each other's throats for the honor of discovery of *Collodion* — or what is termed in Buffalo the "new *Boston notion*" — hope that its parentage will be settled with less discussion and ink-shed than in the instance of the letheon. — Dr. Charles A. Greene of Millbury reports having seen last summer in Western New York, a young woman who had but three fecal discharges in nine years. She has but little physical strength. Her heart beats like an infant's, her respiration is peculiar, and so slight is the effort that it is hardly distinguished by a careful observer. There has been an attempt on the part of the physicians in her neighborhood to remove the underlying difficulty (whether it be a partial stricture of some part of the intestines, or a want of action in them, is unknown) but in vain. Oliver in his Physiology, makes mention of some persons having no discharge in one year, but no instance like the above has he ever found recorded. — Dr. T. J. W. Pray of Dover, New Hampshire reports the case of a Mr. Thompson, 35 years old, long subject to fits of intoxication. For five days previous to examination he had been in a beastly state of inebriation; and indeed it was found, upon inquiry, that he had drank in that time *two gallons* of "West India rum." At the expiration of the fifth day he wished medical aid. He seemed not to require any active medical treatment but rather the *expectant* plan, and he was depleted a very little for an experiment. The blood was forthwith drawn; and it was found destitute, in a measure, of its watery elements — alcohol having been substituted therefor. Immediately a lighted taper was applied to it, and it began to burn with a flame similar to that of alcohol. The fact that the blood did burn was substantiated by various respectable citizens of South Berwick who were eye-witnesses at the time the blood was drawn, and saw the experiment tried. The conflagration produced such an effect upon the patient that he refrained from his intemperate habits, and afterwards became a more sober man. — At the meeting of the American Medical Association in Baltimore, Dr. Holmes of Boston, of the Committee on Medical Literature, read a lengthy report, and very amusing withal. The report embraced a rather scathing review of American Medical Literature. The doctor was employed nearly two hours in reading it. It was laid upon the table. — The Annual Meeting of the Massachusetts Medical Society, which is the most interesting medical convention in New England occurs on the last Wednesday in May. At 10 o'clock A.M., the members assemble at the,

Masonic Temple, Tremont Street, for the transaction of business. After the election of its Counsellors, and the delivery of a discourse by Dr. L. V. Bell, they will dine together at Faneuil Hall, the renowned cradle of liberty. — Extracted from the *Boston Medical and Surgical Journal*, April–May, 1848.

R. F.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS

The June schedule for Consultation Clinics for Crippled Children in Massachusetts under the provisions of the Social Security Act follows:

Clinic	Date	Clinic Consultant
Salem	June 7	Paul W. Hugenberger
Haverhill	June 9	William T. Green
Brockton	June 10	George W. Van Gorder
Lowell	June 11	Albert H. Brewster
Greenfield	June 14	Charles L. Sturdevant
Springfield	June 15	Garry deN. Hough, Jr.
Pittsfield	June 16	Frank A. Slowick
Worcester	June 18	John W. O'Meara
Hyannis	June 24	Paul L. Norton
Fall River	June 28	David S. Grice

Physicians referring new patients to clinics should get in touch with the district health officer to make appointments. Patients are seen by appointment only.

MISCELLANY

BOSTON LYING-IN HOSPITAL

Mr. Richard D. Mills has been appointed administrator by the trustees of the Boston Lying-in Hospital. Mr. Mills, who served as a supply officer during the war, has been administrative assistant at the University Hospitals, Cleveland, and, since 1946, administrator of the Suburban General Hospital, Bellevue, Pittsburgh.

CORRESPONDENCE

SPONTANEOUS PNEUMOTHORAX

To the Editor: The article by Dr. Ralph M. Myerson entitled "Spontaneous Pneumothorax," which appeared in the April 1 issue of the *Journal*, recalls a personal experience with this condition that may be of educational interest. While stationed with the United States Army in Bavaria, Germany, I was privileged to attend 2 cases and heard of a third case of spontaneous pneumothorax occurring in apparently healthy persons. All patients were young men — 2 American and 1 German. Each occurred while the patient was skiing in the nearby Alps and was not, so far as could be determined, related to any falls or mishaps that accompany participation in this sport. Subsequent disposition of the 2 cases observed made follow-up studies impossible, but thorough examination at the time, aside from positive x-ray findings of the pneumothorax, failed to reveal any underlying or previous lung disease. An inquiry of a German physician indicated that such an occurrence is not too uncommon in the non-indigenous or inexperienced skier coming to that mountain area.

In view of the above experience two points arise for consideration. A rarely considered factor in the precipitation of spontaneous pneumothorax is described. Spontaneous pneumothorax in apparently healthy persons resulting from the decreased atmospheric pressure associated with airplane ascents and altitude-chamber studies is known to occur. That an inherent weakness in the pleura or the presence of a superficial pleural bleb is a prerequisite is generally assumed in all cases of spontaneous idiopathic pneumothorax. In addition to the hyperventilation and increased depth of respiration attending a decrease in atmospheric pressure, skiing superimposes the strain of strenuous exercise and motion of the arms and chest. This exertion may have been the only factor in the cases cited. But the fact that 2 of the cases and probably the third definitely occurred in apparently healthy persons under identical conditions implies that atmospheric pressure had a strong contributory effect. Secondly, it would be of interest to compare the incidence of spontaneous pneumothorax in healthy persons subjected to unaccustomed altitude variations similar to that in the cases cited above. Thus far, knowledge only extends to the influence of atmosphere under passive conditions. It may be necessary to make some revision in the statistics pertaining to this condition regarding both overall frequency and the particular locale studied.

Thomas F. Frawley, M.D.

Buffalo, New York

BOOK REVIEWS

Reading and Visual Fatigue. By Leonard Carmichael, Ph.D., and Walter F. Dearborn, M.D., Ph.D. 8°, cloth, 483 pp., with 103 illustrations and 6 tables. Boston: Houghton Mifflin Company, 1947. $5.00.

This book presents an excellent review of the literature on reading and visual fatigue, as well as the results of extensive new experimentation on these subjects conducted by the authors' associates. The Committee on Scientific Aids to Learning made financial grants to Harvard University and Tufts College to undertake the studies presented.

The first half of the book reviews in some detail the literature on visual fatigue and reading, the problem of illumination, blinking and the recording of eye movements. The second half describes experiments in which 40 high school and college students read for periods as long as six hours. During the reading continuous recordings were taken, providing an electroencephalogram, a horizontal electroculogram, a vertical electroculogram, an electrocardiogram and a record of page turns. The instrumentation appears to have been excellent, and the statistical analysis competent.

The results of the investigation support the modern view that "eye strain" is of central origin. The authors make the following statement:

> The most important fact about reading for long periods as shown by the laborious recording and statistical techniques of these experiments is not a specific change in physiological mechanism. It is not a change in eye muscles, for example. Rather, the basic variable which seems to determine the presence or absence of changes during work done in long periods of time and which can be described as "fatigue" is a general characteristic of the subject's whole attitude toward his task.

The eye muscles are so much more powerful than is necessary for even prolonged reading that "the first index of fatigue seems to come in the alterations of the general attitudes and general feelings of the subject, not in a breakdown of the sensory-neuromuscular mechanism which actually performs the task."

The book should be of particular interest to all who are concerned with visual education.

Stereoscopic Atlas of Neuroanatomy. By H. S. Rubenstein, M.D., Ph.D., and C. L. Davis, M.D. 4°, boxed, 19 pp., and 43 stereoscopic plates. New York: Grune and Stratton, 1947. $10.00.

This atlas was designed primarily for the use of students and physicians taking a refresher course in brain anatomy. It consists of forty-three single plates, and a small pamphlet, comprising a dissection manual and an index to the plates. Each plate has a lettered localization diagram in addition to the photographic reproduction of brain structure. The art work is good, and the atlas should prove valuable to interested persons.

(*Notices on page xix*)